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Introduction to the Published Program of the Fifth Annual Meeting of The American Society of Human Genetics

THE American Society of Human Genetics held its fifth annual meeting at Cornell University, Ithaca, New York, September 7–10, 1952. The meeting was well attended and a stimulating program was presented. Part of this program is published in this issue. Appearing are the president's address, comments on the relation of Human Genetics and Medicine by outstanding leaders in the medical profession, several symposium papers, two panel discussions, a few of the many short scientific papers which were presented at the meeting, the secretary's annual report and a 1952 membership list. Also appearing are several articles and book reviews which were on the editor's desk prior to the time of the annual meeting and, last but not least, the bibliography of recent and current literature on human genetics which has become a standard feature of each issue. Papers given at the annual meeting but which did not reach the editor's desk in time for inclusion in the present number will be considered for publication in subsequent numbers.

In addition to the above general comments, a few statements relative to the society's inception and its later history will be presented in these introductory remarks. It seemed that such outline statements might serve as a desirable background for the society's fifth annual program—especially to new members or to non-member readers.

The American Society of Human Genetics had its first tangible beginnings in 1947 when a few geneticists got together at Chicago to discuss what might be done to encourage the development of human genetics in America. Several plans of action were considered. Finally these geneticists concluded or agreed that the only plan which seemed to hold any promise of success was one which called for the organization in America of an independent human genetics society and the publication of a journal in which all, or at least most, American articles on human genetics might appear.

These interested geneticists recognized that if any plan, such as the one indicated above, was to be put into effect, someone would have to take the lead. They were willing to sacrifice time for this, but before initiating direct action they wanted to know how desirable and feasible the proposed plan appeared to several hundred other persons in America who were known to be interested, to some extent at least, in human genetics. So they called an informal meeting at Chicago during the 1947 A. A. A. S. convention. About 150 persons attended. In addition, they sent letters of inquiry to about one hundred other interested persons in America, i.e. persons who had not been able to attend the informational meeting at Chicago. The responses which they received from every source were overwhelmingly favorable. Hence they felt sufficiently encouraged to warrant the initiation of their plan. By early spring of 1948 they began sending invitations for membership in the proposed society. A fee of $2.00 was arbitrarily charged for organizational purposes. By June of 1948 the number of invited persons who had responded favorably was so large that it seemed certain that a human genetics society in America was going to become a reality. The time, consequently, appeared ripe for the election of officers who would assume final organizational responsibilities. A slate of officers was prepared by a nominating committee. Ballots were mailed to all who had indicated an interest in the proposed society to the extent of sending the $2.00 organizational fee. Nearly all of the distributed ballots were checked and returned. Tellers were appointed who counted the returns and reported the results. The following persons were shown to have been elected: President: H. J. Muller, Indiana University; Vice-President: L. H. Snyder, The University of Oklahoma; and Secretary-Treasurer: Herluf H. Strandskov, The University of Chicago.

Upon election these officers immediately arranged for an organizational meeting to be held at Washington, D. C. early in September 1948. The meeting was held as scheduled. About 50 persons

attended. H. J. Muller presided. The first item of business was a consideration of the constitution which had been prepared and circulated prior to the time of the meeting. After some discussion and revision it was adopted. Then and there The American Society of Human Genetics, as a formal organization, came into existence. The three members who had been elected to office at an earlier date by the informal group were unanimously declared the first officers of the new society. They were instructed to hold office through the remainder of 1948 and the whole of 1949. Many additional items of business were considered at the organizational meeting. Among these the one which loomed as the most important was the one which pertained to the publication of a journal. The constitution which had been adopted provided that the society should publish a quarterly journal of human genetics, but opinions differed as to the time when this provision should be put into effect. The members present finally voted that the journal should appear at the earliest possible moment. C. W. Cotterman was asked to serve as its first editor which implied that he should also be responsible for all details leading to its establishment.

Immediately following the 1948 organizational meeting the secretary-treasurer started a drive to obtain new members and independent subscriptions to the proposed journal. The drive was continued through the spring and summer of 1949. At the start of the year the drive was very successful but by late summer its effect was dampened somewhat by the fact that some of the secretary-treasurer's promises, especially those pertaining to the time of appearance of the journal, were not being fulfilled. These failures not only made the drive more difficult but resulted in what seemed like an endless number of inquiries from members and subscribers regarding the time of appearance of the first issue of the journal. The inquiries which demanded responses added to the already heavy load of the secretary-treasurer, but the goal to be achieved appeared so important that no amount of sacrifice of time and effort seemed at this time too great.

During these same ten or twelve months, C. W. Cotterman was laboring desperately to secure good manuscripts for the first issue of the proposed journal and to locate a satisfactory printer. He was also confronted with many details relative to type, format and general appearance of the journal. All of these problems required more time than had been anticipated, but finally by September of 1949 the first issue of the journal appeared. Everyone was elated. The contents were excellent. The editing was superb and the style, format and general appearance of the Journal were most pleasing. Cotterman especially was to be congratulated.

The second or December issue of the journal arrived a few months later. It was equally laudable in every respect. Since the September and December issues were published at the close of the society's fiscal year they automatically came to constitute the whole of Volume 1. (All later volumes consist of March, June, September and December numbers.)

Late in December of 1949 the second annual meeting of the society was held at New York City under the joint auspices of The American Association for the Advancement of Science and The American Institute of Biological Sciences. About one hundred members attended. President Muller presided at the business meeting. Many encouraging reports were presented, but the one which raised hopes the most was one which announced that the society had received a grant in the amount of $4,000 from the Coolidge Foundation of New York, N. Y. The society was extremely grateful, because without such support its journal could not have been continued. The various scientific programs which had been arranged for the annual meeting were unusually good and exceptionally well attended. President Muller's excellent presidential address entitled "Our Load of Mutations" drew a large audience. It appears in the June issue of Volume 2.

During the spring of 1950 a second drive for new members and independent subscribers was begun. Especially encouraging were responses from many members of the medical profession and from a large number of medical libraries. The drive was continued through the summer of 1950. Early in September of 1950 the society held its third annual meeting at Columbus, Ohio in conjunction with the celebration of the Golden Jubilee of Genetics which commemorated 50 years of Mendelian Genetics. L. H. Snyder was the society's president. His presidential address was part of the Jubilee program. He spoke on the subject of "Old and New Pathways in Human Genetics." The address appears in the March issue of Volume 3. It was particularly fitting that L. H. Snyder happened to be the society's president at the time of the celebration of 50 years of Mendelian Genetics, because L. H. Snyder had been one of the most active of human geneticists in America during the latter half of this period.

With the start of the year 1951 a third attempt was made, on the part of the secretary-treasurer, to obtain new members and subscribers. This drive was particularly encouraging in that it brought a fair number of foreign corresponding members and of foreign institutional subscriptions in addition to American active members and subscribers. Despite these encouraging results it was clear that the total number of members and independent subscriptions was not as yet large enough to carry the printing cost of the journal. Outside funds had to be obtained. Appeals were made to foundations and individuals. Fortunately, one member of the society, who wishes to remain anonymous, was sufficiently interested in the cause of the society to contribute $4000 towards its support. The society was and remains grateful to him for coming to its aid at this particularly critical time in its history. His gift raised everyone's hopes and made the planning for the society's future course of events much easier. The fourth annual meeting of the society was scheduled and held in September of 1951 at the University of Minnesota, Minneapolis, Minnesota, under the auspices of The American Institute of Biological Sciences. The scientific sessions were well attended. President L. R. Dice spoke to a large audience on the subject of "Heredity Clinics: Their Value for Public Service and for Research." His address is published in the March number of Volume 4. The topic selected by President Dice was a most appropriate one for him because he had been largely responsible for the development of the Heredity Clinic at the University of Michigan, Ann Arbor, Michigan, which by then had become one of the leading heredity clinics in America.

With the beginning of 1952 several important changes occurred relative to the society. The secretary-treasurer's office which had been a joint one, and held much too long by the original secretary-treasurer, was now separated. S. C. Reed, of the Dight Institute of Human Genetics, Minneapolis, Minnesota became the secretary of the society, and C. Nash Herndon, of the Department of Medical Genetics, Bowman Gray School of Medicine, Winston-Salem, North Carolina became the treasurer. This division was provided for by the constitution and was a most necessary one because the duties of the single or joint office had become far too time consuming for one person. The infusion of new blood, of the most appropriate type, resulted immediately in accelerated activity. An intensive drive for new members and subscriptions was inaugurated. This drive was highly successful. Yet it remained clear that outside funds would still be needed—partly to finance the journal and partly to carry on a really intensive membership and subscription drive which once and for all would put the society and its journal on a self-sustaining basis. Appeals were made. By late summer an announcement occurred to the effect that the society was the recipient of a grant of $4,200 from the Rockefeller Foundation. An acknowledgment of this recent and much appreciated support appears in this issue.

A second major change in the society's official personnel which occurred at the beginning of 1952 pertains to the editorship of the journal. At the 1951 annual meeting C. W. Cotterman announced that he was resigning as editor effective December 31. Everyone regretted this announcement because everyone recognized that Cotterman was a superb editor. In the short span of three years he had established for the society's journal a most enviable reputation. His ability as a statistician and his masterful knowledge of genetic principles had been applied effectively to many manuscripts. However everyone also recognized that Cotterman had been devoting far too much of his time to the journal and that he deserved to be allowed time once again to carry on research and to publish scholarly papers of his own. Hence his resignation was accepted. To fill the vacancy the Board of Directors of the society elected the writer of these remarks. He was reluctant to accept the responsibility, first of all, because he knew that he could not fill Cotterman's shoes, and secondly, because he had already given three years of his time to the office of the secretary-treasurer. Despite these facts he acceded to its request because to him the success of the society and its journal was and remains a matter of first importance. He recognizes that he may not be able to maintain for the journal the standard set by his predecessor, but he will try. He can hope to approach it closely if investigators in America, or in any other part of the world, will submit manuscript of high quality which also are meticulously prepared for publication in accord with the journal's policies. He will also try to have the journal appear on time. This goal has not quite been reached this first year under his editorship but it has been approximated. He hopes that it will be attained very soon and that it will then be maintained.

The events reported so far take us to the time of the fifth annual meeting of the society, held at Ithaca, New York, September 7–10, 1952. This meeting was in many respects a most memorable one. In the first place, it was held on the beautiful campus of Cornell University and under ideal weather

conditions. The meeting arrangements were excellent, the credit for which must go largely to the staff of the American Institute of Biological Sciences and to the society's local committee. The hospitality of Cornell University and of the city of Ithaca was also of the finest. The scientific program arranged by the society's committee was pleasantly varied and exceedingly stimulating. For the first time in the society's history arrangements were made for an evening dinner at which time and place the society's outgoing president gave his address. About 150 members and guests attended the dinner. President Kallmann spoke on the subject of "Human Genetics as a Science, as a Profession and as a Social Minded Trend of Orientation." The address is published in the present issue. Following his address the society was honored by remarks from several outstanding leaders in the medical profession. Among those who spoke and whose comments are published in this issue were: Dr. Lester J. Evans, The Commonwealth Fund, New York, N. Y., Dr. Currier McEwen, Dean, New York University College of Medicine, New York, N. Y., and Dr. Edward T. Wentworth, President, Medical Society of the State of New York, Rochester, N. Y.

As was stated in the opening paragraph several symposium papers and panel discussions presented at the meeting are also published in this issue. We cannot take the time nor the space to comment about each one. We invite everyone to read them.

In bringing to a close these introductory remarks to the published program of the fifth annual meeting of the American Society of Human Genetics, it seems appropriate to emphasize that there appears to be abundant evidence that the society at the time of this, its fifth anniversary, has already served fairly respectably the functions for which it was organized—namely the furtherance of sound human genetic research and the dissemination of sound human genetic knowledge.

The society's president for 1953 is C. P. Oliver of the University of Texas. Under his leadership the society should continue to grow steadily and to serve its functions honorably.

HERLUF H. STRANDSKOV, Editor
The University of Chicago

Human Genetics as a Science, as a Profession, and as a Social-Minded Trend of Orientation[1]

FRANZ J. KALLMANN

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EVERY scientific society in good standing treasures its share of expert statisticians and semantically-minded purists, and the American Society of Human Genetics is no exception. Consequently, there is still some disagreement as to whether this is the fourth or the fifth anniversary of our Society, although its first public appearance is known to have taken place in 1948. According to the purists, the term "anniversary" refers to the recurrence in each year of the date of an event. It seems, however, that our founders failed to register a precise birthday as the event to be commemorated. It is certain only that the Society is still prodigiously young, and that this is its fifth annual meeting, and the first official dinner meeting. It is undeniable, too, that the choice of an appropriate topic for this festive occasion has not been an easy task.

Retrospectively, I may be inclined to concede that the selection of a nutritive topic for this address was almost as difficult as that of helping to guide toward maturity an organization still afflicted with a few minor growing pains. In allegoric terms, the roots of my dilemma might be compared with the embarrassment of a professional baseball player who, in football, never advanced beyond the status of a substitute on his college team, but at a class reunion found himself elected to speak in celebration of this team's championship record. If one prefers to describe the difficulties of the original assignment in a more direct way, one might point to those liabilities awaiting the wearer of a bright-colored cap of maintenance, embellished with the feathers of such noted pioneers of human genetics as H. J. Muller, Laurence H. Snyder, and Lee R. Dice.

It is conceivable that a few compensatory and possibly non-negotiable assets might have been derived from those benefits, which were apt to accrue from the specialized training of a psychiatrist. For instance, certain aptitudes as evolved by that training might have been helpful in an effort to search for a selected assortment of hidden personal motivations behind the solid scientific achievements of my honorable predecessors. Apparently, playful indulgence in such personalized research procedures is rapidly developing into a favorite pastime of some of our fellow scientists. In my special emergency situation, however, there was little likelihood that even the most subtle disclosures would have

Received September 2, 1952.

[1] Presidential address delivered at the fifth annual meeting of the American Society of Human Genetics at Cornell University, Ithaca, New York, September 9, 1952.

saved me from being classified as just another geneticist. As you know, the given classification is still likely to be identified with that sinister version of a reactionary, who is eager to displace despondent sentiments of fatalism and wishful incredulity as symbolized in India by the worship of Siva, the Destroyer. I readily decided, therefore, to approach my topical problem with a straight appraisal of the actual contributions of the three men who had preceded me in office, rather than with a problematic dissection of their personalities.

Pursuing my task in the order of precedence, I had no difficulty in rating our first president, a prominent Nobel Prize laureate, as the man whose experiments on mutant genes had set an everlasting milestone in establishing genetics as a *science*. His leadership attracted outstanding scholars from many different disciplines rightfully concerned with the biology of human health, and he thereby succeeded in laying the foundation to a safe upgrowth of this Society. In line with the unique results of his life work, the message of his presidential address (1950) culminated in a piercing appeal for the recognition of mutation as an alarming cause of disease in man, forever securing his place among the leading scientists of our time.

Equally unchallenged was the choice of our second president as that of an educator, who had carried the torch in the *professional* advance of our discipline. Because of his remarkable success in elevating human genetics to its deserved academic position within the biological sciences, it was entirely fitting that the term of his presidential office coincided with a banner year in the history of modern genetics, the year of its fiftieth anniversary. In commemorating this special occasion with a penetrating account of old and new pathways in human genetics (1951), Dean Snyder's plea for cooperative teamwork in the exploration of human heredity ranked as one of the keynote speeches of the Golden Jubilee of Genetics at his old Alma Mater (Dunn, 1951). From the standpoint of our discipline, the speech tendered a memorable testimonial to the emergence of human genetics as a full-grown profession.

The plainest description of the individual contribution, which typified our venerable third president, was set forth in his high-principled Minneapolis address, entitled "Heredity Clinics—Their Value for Public Service and for Research" (Dice, 1952). With his election, a sincere tribute had been paid to the accomplishments of a competent and conscientious worker, whose concern with the general health aspects of human genetics stemmed from upright devotion to *public service*. His professional orientation had been social-minded in the truest sense of the word, since he always believed in the public responsibilities of our discipline. His call for well-staffed heredity clinics in every state was founded on abounding experience and a scrupulously blueprinted scheme, as he had pioneered in the organization of one of the oldest and most effective genetics departments in the country. In his scheme for district

heredity clinics, the same emphasis was placed on the genetics of superior health and superior mental ability as on the study and care of inherited pathological traits. The functional design of this plan served ably to formalize what seemed to be one of the most creditable objectives of our Society.

When I reached this point in appraising the academic credentials of our principal authorities, it was apparent that the first goal of my own report was to be that of creating a general atmosphere, which would be tempered by a gentle blend of sympathetic and empathic *tolerance* on the part of the membership. The fundamental triad of scientific endeavor, professional competence and social-minded purport had been imprinted on our statutes, and little seemed to have been left that should have been said or might have been done.

In preparing this report, I was tempted for a short time to dwell on the need of giving priority, in man, to the mutative effects and selective values of *mental* traits, apt to be subject to the same genetic principles as demonstrated for scores of essential physical potentialities. However, such a topic of psychiatric coloring was certain to reopen the door to that hoax of a dualistic setting, which contributed so heavily to a crippling division in other scientific disciplines. In fact, the urge to maintain a dichotomy of body and mind seemed almost as harmful as that of splitting a personality, and I soon remembered that psychiatrists were trained to cure schizophrenic phenomena rather than to provoke them.

An antidotal alternative to dualistic discord presented itself in the idea of a concentric drive toward unified progress and intradisciplinary harmony or, more specifically, toward a triadically coordinated approach to a strong and single-minded discipline of human genetics. There was little doubt that we were marching along the proven pathways of scientific pursuit, professional prowess, and social conscience. What remained to be achieved, however, was the forging of a solid band around the various groups of specialists combined in the Society—a band of *friendship* emboldened by *singleness of purpose*.

For obvious reasons, our members had come from many different branches of science; from biology and mathematics, from psychology and medicine, from anthropology and the social sciences. Most of these fellow members earned a living in professions far removed from experimental genetics as studied in plants or animals. A majority had spent years of plodding hardship in militant minority groups within their particular specialties, and some of us had grayed in holding the fort against a tide of overenthusiastic generalizations derived from pseudo- or supertotalitarian beliefs in the self-perpetuating or government-directed omnipotence of human cultures. It was understandable, therefore, that the spirit which prevailed in this Society during the first few years of its existence gravitated in the direction of intellectual individualism mixed with pronounced caution.

However, when it is time for cadres to form an army, final victory depends

on the acceptance of a *common cause* and a *common emblem*. Since a certain lack of imagination has made me rather pragmatic and generally susceptible to notions of economy, at least in societal affairs, I was led to believe that the problem of an emblem might partly be solved by establishing the precedent of an *annual dinner*. This was the reason why a dinner meeting was arranged at Prudence Risley Hall. Evidently, its immediate purpose was to afford our members an opportunity to meet in pleasant surroundings and therein to talk of our common cause. It also was my hope, of course, that the atmosphere of good fellowship created by a good dinner might be helpful in generating the previously solicited attitude of indulgent gentleness toward presidential reports.

Strictly in terms of the future solidarity of the Society itself, it may not be too important at this point whether it will actually be feasible to uphold the expedient of an annual dinner long enough to let it grow into a truly emblematic tradition. In no respect will it be possible, however, to question the need of building a well-fortified platform for the conduct of our *common cause*.

This statement does not mean that we have not always had a good cause or have not always been aware of it. Nor should the plan of a good *societal platform* be interpreted in the sense of that politically-minded train conductor who used to tell his passengers that "a platform is to get in on—not to stand on." The platform to be built by us should be for every old member to stand on, and for many new members to get in on from the various specialized disciplines interested in the genetics of human health. It should be steadfast, and at the same time sufficiently wide to function like a bridge: A bridge over intradisciplinary diversities, real or imaginary; a bridge over interdisciplinary dividing lines, visible or invisible; in short, a bridge leading to unity and prosperity in the one field of interest which we all have in common, *human genetics*.

In a detached approach to the understanding and management of potentially disruptive lines of division, one would be in error to over-rate *intra-group diversities* derived from different temperaments, talents and personalities or those derived from differences in educational backgrounds, personal attachments and taboos. In line with general genetic principles, such diversities exist in every human group which is formed for purposes of specialization or socialization. Fortunately, they abound in this organization, too. Without diversities of this kind, we would fail to disagree, and a society lacking differences of opinion is certain to stagnate and to disintegrate, at least in an imperfect reality.

Other dividing lines within our discipline, usually more apparent than real, are cast by the shades of *professional sensitivities* precipitated by conditioned defense reactions to presumably organized hypocrisy. The apparent need of such self-protective designs is traceable to the fact that we are late-comers in

the boundless field of public health and, therefore, are beginners in the skills required for competing in a vast and frequently shifting area of operation.

The crux of joining very old professions such as medicine, which is proud of being no longer merely an art but principally a science (Bauer, 1952), is likely to be intensified by an early realization that the natural expansion of our total field of activity does not preclude the necessity of prolonged efforts for every square inch of its conquest. The impact of this experience easily leads to feelings of ambivalence or to slightly distorted concepts regarding the size of our competitive share apportioned as a premium for cooperation with other sciences. In consequence, many of our research workers tend to lean toward academic skepticism and professional superspecialization, frequently expressed in the form of a *pessimistic* preference for the tools rather than the prospective beneficiaries of our investigative work.

Since geneticists are generally as human as the immediate objects of their research interests, one may concede that timid withdrawal into sheltered laboratories is a tempting alternative to the threat of being drawn into a whirlpool of crusading campaigns purporting to serve the needs of public health. However, general health and preventive medicine are apt to be *community affairs*, irrespective of the fact that the individual physician must think of medical care as his primary duty and largely in terms of the recovery of the patient who is ill (Master, 1952). From the standpoint of public health, therefore, the prudish pessimism of a fact-finding research geneticist is liable to create the impression of a cynical defense modality (Janse de Jonge, 1952) and, by way of paraphrasing a dictum of Heidegger, appears like a nonauthentic way of human life or of a science dealing with the secrets of human life.

No redundance is necessary in acknowledging the truism that a strictly scientific search for the facts and potential implications of human heredity will always be our chief objective. On this basis it should be clear to us, however, that the purpose of knowing the "Secrets of Nature" is not to establish some absolute value which can be dissociated from man's emotion or, in the words of Sherrington (1951), which can be applied without "altruism as passion." In a biological science such as human genetics, rationality is "a tool for thinking" rather than "mere worship of Reason." It is disillusioning to deal with human problems in an entirely abstract manner, and little can be gained by a science of human genetics which neglects the *human element* or the import of *altruism* as "the greatest contribution made by man to life."

In order to satisfy what Sherrington called our "inalienable perogative of responsibility," we should make certain in the training of future workers in human genetics that adequate understanding of human behavior and a profound sense of social obligation be given equal rating with scientific skill and scholarly ingenuity. Without empathy toward the phenomena of human im-

perfection, human decency and human apprehension, we may be successful in making scientific contributions to the advance of an increasingly specialized knowledge of man's heredity, but we would not succeed either in communicating or in applying that knowledge (Kelly et al., 1952). In particular, we would often find ourselves at odds with the growing tendency of modern societies to sacrifice family pride and individual independence for the impersonal gift of mutual security provided by a formalized version of the welfare state (Alexander, 1951).

Fortunately, there is no reason for assuming that a well-trained student of human genetics cannot at the same time be *social-minded*, *professionally competent*, and *scientifically proficient*. The need for skepticism in this respect is refuted by the history of biology and by the records of enlightened humanitarianism made by scores of great biologists. It has long been possible and, I hope, will always remain possible to specialize in one of the life sciences without acquiring the psychology of a "microcosmic" world, recently described as the state of mind of a distrustful biologist distinguishing himself by a high degree of resistance to lollipops and the social sciences (Bates, 1952). For instance, a student of biology should be able to learn both the principles of mathematical statistics and the mechanics of working a punch card machine in connection with people's measurements and correlation coefficients, without being in danger of losing humility or the broad perspectives of human frailty and faith.

If one chooses at this point to record a factual issue of potentially instructive significance, Bates (1952) has probably been correct in observing that in comparison with biology "the science of medicine reflects in some measure the unity of the profession of medicine." Historically, it also is safe to infer that the organizational problems of biology have been "different from those of chemistry or medicine." It is doubtful, however, that the successor of medical men in maintaining a united professional front can be attributed chiefly to their desire "to keep up with the lawyers, bankers, soldiers and so forth."

Even if this utilitarian explanation is offered only as a fact-trimming attempt at oversimplification, it utterly underrates the traditional fact that competent physicians have been unified by *the idea of a common cause*. The skeptics among biologists and other groups of scientists may be disinclined to trust the earnestness or the originality of that cause. However, the price to be expended for their disbelief will be costly and comparable to the one exacted by indifference to pressing community affairs. According to Plato, the penalty paid by good men for refusing to take part in government is to live under the government of bad men. By analogy, one may expect that the qualifications of scientists and practitioners, working in a branch of medicine during a certain era, will be determined somehow by the reliance placed by their contemporaries on the Hippocratic ideal of a "universal language of the heart" (Johnstone, 1951).

It is contrary to this essential principle to view problems of human health or disease with irreverence towards the "love of man" (Greer, 1952).

In the evolution of a strong and widely trusted discipline of human genetics, we must be ready to take the same *burning pride* in our responsibility for the major purposes and central problems of human beings and their societies, that has long been considered to be a vested privilege of good medical men and good public health workers. It would not be reasonable to contend that profundity in the understanding of predominantly medical problems of human heredity is contingent on some special technical aptitudes fostered by medical training. I am of the opinion, however, that without trust in the ethical equivalents of Hippocratic ideality, neither a medical nor a non-medical specialist can be certain of applying his expert knowledge of human genetics in a productive manner, that is, in a manner "applicable to the extension of life and to the improvement of productivity during life" (Lemkau, 1952).

If a broad moral platform is adopted for the discharge of the social and professional responsibilities of our discipline, it will not only be helpful in rallying a multitude of specialized groups around a common cause, but it will serve to vitalize the *general appeal* of our cause. The prospect of taking an active part in such a promotional scheme may not seem attractive to a scientist, who is glued to a microscope or is brooding over the structural essence of life. In view of the growing complexity of human societies, however, it is apparent that our chance of inducing the employment of sound biological principles in future population and public health policies will depend on the efficacy of our joint promotional plans and endeavors.

In my humble opinion, it will be advisable to organize societal drives in several directions. Apart from the emphasis which should be placed on improving the general *humanization* and *comprehensibility* of genetic theories as applied to man, much attention should be given to the careful *selection* and systematic *training* of future workers in human genetics. As is true for any other group of specialized guidance workers in the field of public health, a genetic counselor should be selected from the standpoint of both professional qualifications and personal integrity. While in training, he should have ample opportunity to gain practical experience in dealing with people in distress, and he thereby should be taught to broaden his frame of reference from genetic to human problems. He should learn in practice rather than from books that there is no stereotyped formula in any sector of genetic counseling work, on which he can automatically rely for appraisal of the degree of a person's maladjustment within the social setting in which that person lives (Stokes, 1952). It is regrettable, therefore, that little progress has been made in the organization of a diversified post-doctoral fellowship program for the training of qualified biologists, psychologists and medical men who are desirous of specializing in human genetics.

The aim of another line of promotive effort should be to make certain, and to make known among professional workers with a potential interest in human genetics, that their participation in the activities of this Society not only is feasible, but is *welcomed* by all of us with open arms. Considering the magnitude and the multiplicity of the scientific and professional tasks ahead, we are likely to derive a more substantial gain from a liberal membership policy centered on the qualities of professional competence and social consciousness than we might from a poorly concealed trend toward an inbred fraternity of pure-line scholars. If we want to take our place in the big family of professional confederations concerned with human welfare and public health, we will need the scientist as well as the medical practitioner, the psychologist as well as the statistician, the specialist as well as the family physician. It is obvious, too, that this all-inclusive scheme of cooperative organization should find its noticeable reflection in the *editorial policies* of the standard bearer of this Society, the American Journal of Human Genetics.

Of similar importance is a set of promotive objectives relating to a question, which is likely to be raised especially with reference to the economics of our long-term research and public health activities. The question concerns the *practical value* of our work and, even if sometimes biased or otherwise distorted, should not be ignored by us. Fortunately, the woodlands to be covered by our discipline are so full of valuable trees that no real difficulty is created by any question conveying a complaint about the forest's dearth of visibility. The only difficulties which could possibly be harassing in this respect are those which may arise either from some preconceived notions of our own making or from a timid failure to lay sufficient stress on the *positive health aspects* of human heredity.

It is a plain but easily misjudged fact that in relation to human health and personality development, hereditary influences are thought of as static, while environmental influences are believed to be amenable to almost infinite manipulation. Actually, there is no single force in man's life and struggle for existence, which is more powerful, more dramatic or more inspiring than the one derived from the *dynamics of human heredity*.

It would be useless to deny that serious *pathologic* deviations may be produced by certain mutant genes. It is also true, however, that the prevention or therapeutic correction of the resultant condition will be aided immeasurably by an adequate understanding of the alternative functions of the normal and mutant genes involved. It is equally correct to state that the *main elements* of heredity are inseparable from man's evolutional advance, from his adaptive strength, and from his hope for continuous posterity and future welfare.

As a *science*, therefore, human genetics is basically identified with a belief in orderly patterns of progress and evolution, and is apt to act as an antidote to the excitement of rebellious anguish, revolutionary destructiveness or supernatural symbolism in frustrated people. In other words, genetic knowl-

edge casts light on certain limitations of the human status, but it throws no gloom on any endeavor directed toward superhuman development.

As a *profession*, workers in human genetics are compelled to advocate a coordinated approach to the totality of human organisms as indivisible entities. In the organized management of problems of general health, culture and prosperity, they aim at giving encouragement to a person's feeling of responsibility for his own self, without fostering any tendency to independence of the group criteria of good and bad. In fact, the basis of genetic work in man is interlinked with the concept that the family is indispensable as a biological, social and educational unit.

As a *general trend of orientation*, familiarity with the principles of human genetics does not suffice to insure immunity from cliché generalizations or excess emotions as regards universal imperfections of human existence or the deeper meanings of human inequality. Some of this knowledge is certain, however, to be beneficial in forming such constructive ideas of health, sanity and social order, as may flow from realistic images and a laborious search for lasting values.

Hence, since truth is considered to be the daughter of Time, we should have no hesitation to expound genetic phenomena in man as a potent safeguard of *public health* and as a token of *promise for the future.*

REFERENCES

ALEXANDER, F. 1951. *Our Age of Unreason; a Study of the Irrational Forces in Social Life.* Philadelphia: J. B. Lippincott.

BATES, M. 1952. Where is biology? *A.I.B.S. Bullet.* 2: 15–17.

BAUER, L. H. 1952. Medicine and the problem it faces. *N. York State J. M.* 52: 1806–1808.

DANFORTH, C. H. 1923. The frequency of mutation and the incidence of hereditary traits in man. *Eugen., Genetics and the Family.* 1: 120–128.

DICE, L. R. 1952. Heredity clinics: their values for public service and for research. *Am. J. Human Genet.* 4: 1–13.

DUNN, L. C. 1951. *Genetics in the 20th Century.* New York: Macmillan Co.

GREER, A. E. 1952. Evolution of medicine. *J. Am. M. Ass.* 148: 103–105.

JANSE DE JONGE, A. L. 1952. The psychology of pessimism. *Folia Psychiat. Neurol. at Neurochir. Neerl.* 55: 20–41.

JOHNSTONE, R. T. 1951. Medicine can bridge the sullen tide. *J. Am. M. Ass.* 147: 911–913.

KELLY, E. L. et al. (Committee on Relation between Psychology and the Medical Profession). 1952. Psychology and its relationships with other professions. *Am. Psychologist.* 7: 145–152.

LEMKAU, P. V. 1952. Toward mental health. *Mental Hyg.* 36: 197–209.

MASTER, A. M. 1952. The problem of medicine. *N. York Med.* 8: 16–29.

MULLER, H. J. 1950. Our load of mutations. *Am. J. Human Genet.* 2: 111–176.

SHERRINGTON, C. 1951. *Man on his Nature.* Cambridge: The University Press.

SNYDER, L. H. 1951. Old and new pathways in human genetics. *Am. J. Human Genet.* 3: 1–16.

STOKES, W. R. 1952. The concept of emotional maturity as related to marriage counseling. *Marriage and Family Living.* 14: 127–130.

Human Genetics in Relation to Academic and Public Health Education[1]

1. The Changing Scene of Medical Education

NEITHER the character of the change in the setting of medical education nor the rate of change can be clearly stated at the moment. There is no doubt that medicine is emerging from its most productive era, which began in the latter part of the 19th century. In the mid-20th century we can recognize that the progress in this era stemmed from the scientific foundation of the natural sciences. Medical teaching has prospered in the university teaching hospital and medical research laboratory. While the striking advances of recent years, with which we are all familiar, have been taking place, there has been growing up alongside of medicine areas of new knowledge concerning the nature and behavior of man. Much of this new knowledge is from the fields of social and behavioral sciences. Also, as you people here tonight so well recognize, there have been many new advances in fundamental biology which are now applicable in the study of man.

Medicine is now equipped to deal with "man as a whole" in his natural setting which is society. The ambulant patient is receiving more attention relatively. The expressions "outpatient department," "family," "community," "follow-up," "continuity of study" are all heard frequently in university medical teaching centers. Taken together they indicate that medicine is moving toward study of man in his natural setting which means then that we must draw on all of those areas of knowledge which can contribute to a better understanding of the total behavior of man. If we approach such study broadly we will be dealing with a fundamental biological phenomenon, namely, organism-environment relationship. Genetics will be called upon to participate in the development of new ways of studying the inherent nature of man so that the manner in which man reacts with his environment can be better understood.

The important thing to us tonight is that universities offer every opportunity possible to all their teachers and students interested in better understanding of the nature and behavior of man to work together. Practically, this means that medical schools must reach out into other areas of the university for help in the development of new techniques and methods, among them those deriving from genetics. Also, workers in biology and the social and behavioral sciences will be working more frequently in medical settings where their

[1] Comments by invited speakers at the annual dinner of The American Society of Human Genetics, Ithaca, New York, September 9, 1952.

knowledge and skills can be applied directly to the study of human development and behavior.

Just as the natural sciences enabled medicine to begin to broaden its base of study and service seventy-five years ago, now the new biological knowledge and the social and behavioral sciences enlarge the backdrop against which medicine will continue to grow.

LESTER J. EVANS, M.D.
The Commonwealth Fund, New York, N. Y.

2. Importance of Human Genetics in Medical Education

MR. CHAIRMAN, MEMBERS AND GUESTS: I am sure the importance to the physician of a general knowledge of genetics is so clearly appreciated by all of you that it is unnecessary for me to elaborate on the reasons why a study of genetics should be included in the medical curriculum. These reasons have been admirably stated in the writings of Dr. M. T. Macklin and others. On the other hand, in spite of its importance in medicine the subject of genetics receives little attention in most medical schools. By means of a questionnaire, Robertson and Haley, in 1946, ascertained that in 80% of 60 medical schools a knowledge of human genetics was held to be necessary; yet instruction in the subject was given in only 53% of those schools and in only 11% of them was such instruction given in a systematic fashion. Although, at first sight, this discrepancy may appear inexplicable, it is readily understood by anyone familiar with medical education, for the answer lies in the already overcrowded medical curriculum.

A number of suggestions have been made as to means of correcting the situation. Some have suggested that the principles of genetics should be included as part of the premedical college course. Obviously an introduction to elementary genetics is included in the average college course in general biology; but it is most unlikely that a solution to the problem will be found in more concentrated study of genetics prior to admission to medical school because that would necessitate making genetics a required premedical course and the modern trend, I am glad to say, is toward liberalizing rather than increasing those requirements. Others have suggested the inclusion of formal instruction in genetics as an additional subject in the first or fourth year or both. The objection to this approach has already been mentioned—the curriculum is at present so full that the introduction of new material is difficult to achieve and must be very sketchily presented in the all too small amount of free time which the students now have.

At the New York University College of Medicine, Dr. Donal Sheehan, Professor of Anatomy, has recommended another solution which has the hearty endorsement of our faculty and which it is our aim to put into effect.

Professor Sheehan's contention is that the modern medical school department of anatomy should be changed to a department of human biology with interests and responsibilities far broader and deeper than the study of gross morphology and histology. The detailed knowledge of anatomy which the surgeon and the surgical specialist must have must now be learned in the postgraduate phase of medical education in any case. We believe, therefore, that a considerable part of the student's time in the first year which is now devoted to detailed and systematic dissection of the human body should be deferred, for those who need it, until after the completion of the four years of undergraduate medical work. In the department of human biology, the undergraduate medical student would learn the broad facts of anatomy which are necessary for the understanding of normal and abnormal function and, through the cooperation of the clinical departments, would study those aspects of anatomy which have a clear application to the science of diagnosis. In the time gained through the deferment of detailed surgical anatomy, opportunity would be provided for the study of the biological principles of species and individual variation, of heredity and genetics, the physical and chemical processes of cellular differentiation, structural reactions to environmental change, prenatal and postnatal growth, and the cytological changes in senescence. In such a program the principles of human genetics could be adequately introduced in the first year, while clinical examples and applications would naturally be taken up subsequently in the various clinical departments.

At the New York University College of Medicine we are eager to establish a genetics unit as part of a department of human biology, not only to implement the program of undergraduate teaching which I have outlined but also to enhance research in medical genetics and because of the stimulus it would give to an appreciation of genetic aspects of health and disease to faculty members of all departments.

Aside from the obvious problem of obtaining the necessary funds, there is another practical difficulty which must be overcome from the standpoint of undergraduate teaching. The successful application of the plan necessitates a reduction in the amount of time devoted to the detailed study of anatomy at the undergraduate level. Thus the effort is feasible only if the various medical licensing bodies will be prepared to accept a general rather than detailed knowledge of anatomy on the part of the candidates for medical licensure. I believe the trend is definitely in that direction and that the time is overdue for the broadening of the scope of departments of anatomy so that more of them will become truly departments of human biology.

CURRIER MCEWEN, M.D., Dean
New York University College of Medicine
New York, N. Y.

3. Medicine and Genetics

WERE I a pediatrician, I would say that if your organization is indeed only five years old, it is certainly a remarkably well-developed and lusty child for its age. Almost a case of *pubertas praecox*, which, according to some geneticists may in some cases be hereditary, with possible Y-chromosome sex-linkage. At any rate, it is a pleasure and privilege to extend to you my personal greetings and those of the Medical Society of the State of New York.

The interest of medical men in heredity goes back perhaps to the very beginnings of medicine, when the first doctors took note of the successive appearance of various similar abnormalities or diseases in the same families. But such observations, often accompanied by misguided deductions, had very limited practical value, except, perhaps, to scare the wits out of the individuals and families concerned by the dire warnings which were offered. Even up to a few decades ago, while medical texts were increasingly referring to hereditary factors in diseases, the uncertainties probably out-weighed the certainties, and the value of the knowledge offered was still largely negative, often on the pessimistic, or non-constructive side. All of this may help to explain why, as the science of genetics, and specifically, human genetics, got under way, the medical profession was not as cordial or as interested as it should have been.

Fortunately, we can say today that there has been a change for the better. Not merely has the flow of findings from the new field of human genetics been theoretically impressive, but physicians have been made increasingly aware of how these findings can be put to immediate practical use, to facilitate diagnosis and treatment, to advise patients where there are definite familial threats, and, in thousands of cases, to actually save lives. As a notable example, the knowledge regarding the "Rh" factors—to which two of your members with us tonight, Drs. Wiener and Levine, have so brilliantly contributed—has now become indispensable to modern medicine. In hundreds of other conditions clarification of the role of heredity has also been immensely valuable to physicians in the various specialties. In fact, there is hardly a major disease today for the treatment of which added light on genetic factors cannot bring practical benefits.

However, what has already been accomplished by human genetics, and such acceptance as it has had from medicine, is at best only a beginning, and a portent of how much more can be accomplished. We must face the fact that with respect to most major afflictions—heart disease, cancer, muscular disorders, mental diseases and deficiencies—we are still much in the dark, both as to *causes*—genetic or otherwise—and as to *treatment*. The two are not unrelated. For there is every likelihood that failure to understand the cause

may largely explain failures in treatment. Conversely, the closer we come to an understanding of how heredity, or environment, or both, operate and influence the production of these diseases, the closer we will come to the knowledge required to treat them effectively.

Nor should one place emphasis purely on medical genetics. The good physician will recognize that almost every phase of human genetics—with respect to behavior, external appearance, and every physical and functional trait, normal and abnormal—will have meaning to his practice. It should be his goal to understand the human being as completely as possible, not merely as a physical organism but a socially-functioning individual whose well-being and happiness is tied up with the well-being of society as a whole. And there is perhaps no branch of science today which, if explored as fully as it should be, can do more to help the physician toward a better understanding of patients, and a more effective treatment of their ills, than can the science of human genetics. It is toward that end, that I, as a medical man, would wish to see the fullest possible cooperation between my profession and yours.

E. T. WENTWORTH, M.D., President
Medical Society of the State of New York

Symposium:

The Genetics of Various Constitutional Defects[1]

JAMES V. NEEL, CHAIRMAN

Heredity Clinic, University of Michigan, Ann Arbor, Michigan

INTRODUCTORY REMARKS OF THE CHAIRMAN

OUR three speakers this afternoon will deal with superficially quite unrelated topics. However, it appears to me that there is at least one thread of partial continuity running through these presentations. The term "constitution" which appears in the title of this Symposium is a very loosely used word. It is usually stretched to include the sum total of the intrinsic or innate properties of the human organism, and as such becomes a catch-all term suffering from ambiguity. Strenuous efforts have been made to determine whether the constitution of those who develop, for example, diabetes, differs in any measurable way—to the poor extent that we can now define constitution—from the constitution of those who develop, for example, hypertension. These attempts have met with a certain measure of success, but it must be admitted that references to the "hypertensive," the "ulcerous," or the "diabetic" constitution leave much to the imagination.

In many of the attempts of the past to define constitution, the genetic approach has been largely neglected. It has much to offer. The present papers show why this is the case, and herein lies the thread of continuity between them. Thus, in the field of diabetes there has been an increasing tendency to recognize a number of clinical types of diabetes mellitus. Aside from the rare types, associated with pancreatic destruction, non-pancreatic endocrine disorders, or disturbances of fat storage, two principal forms of diabetes have been delineated, the two together probably accounting for at least 95 per cent of the clinically encountered diabetics. The one type is characterized by obesity, certain rather characteristic anthropometric measurements, a gradual, later onset of clinical disease, a milder course, a relative insensitivity to insulin, and the presence of available plasma insulin. The other group is characterized by an earlier onset in persons who show no particular tendency to obesity or other distinguishing anthropometric tendencies. The disease in these persons tends to be more severe, complicated by the development of ketosis. There is marked insulin sensitivity, and there is no available plasma insulin

[1] The three papers which comprise this Symposium were presented at the fifth annual meeting of The American Society of Human Genetics at Ithaca, New York September 7–10, 1952.

(Lawrence, 1951; Lister, Nash, and Ledingham, 1951; Bornstein and Lawrence, 1951; Draper, Dupertuis and Caughey, 1944).

The thought provoking analysis which Dr. Steinberg will present in the first paper of this Symposium suggests, on the other hand, that the vast majority of pedigrees of diabetes can be explained by a simple (and presumably the same) recessive gene. On a priori grounds, I for one would be inclined to suspect that so complex a disease as diabetes would have several different genetic etiologies. However, Dr. Steinberg's evidence, as that of Pincus and White (1933, 1934) and Hanhart (1950) before him, appears quite convincing. If we accept Dr. Steinberg's findings, then we cannot help but be stimulated by the genetic approach to look about for some explanation of the clinical findings. It occurs to me that the apparently different types of diabetes may be at least in part a phenomenon of human maturation, related to variations in the age of onset of the disease. By age of onset I refer to the very first physiological changes which, as is shown by the birth of oversized babies to potential diabetics 15 to 20 years before the onset of symptoms (Miller, 1945; Kriss and Futcher, 1948; Gilbert, 1949; Moss and Mulholland, 1951), may precede our recognition of the disease by many years. In the further evaluation of this problem the study of the results of the marriage of two diabetics is of especial importance since it is here that the hypothesis of inheritance based on a single recessive gene can most readily be tested. A further problem for the future is the study of the manner in which the two chief clinical types of diabetes referred to above are associated within kindreds and sibships.

Whereas Dr. Steinberg's studies imply a considerable degree of genetic homogeneity in a clinical entity of varied manifestations, the studies of Dr. Adlersberg and his associates suggest important subdivisions of what at first appeared to be a single entity, namely, coronary artery disease in relatively young men, i.e., below the age of 50. They have shown that approximately half of such persons have hypercholesterolemia, and that such persons have relatives who also have hypercholesterolemia (Aldersberg, Parets and Boas, 1949). The possibility is thus suggested that there are several etiologies of coronary artery disease, one of which is a genetically determined hypercholesterolemia. The paper we will hear today represents an important extension of these studies.

Some of the most telling examples of the fruitfulness of the combined clinical, biochemical, and genetic approach are to be found in the field of mental defect. Indeed, it is probably fair to say that the usefulness of the combined approach is as well illustrated and as widely accepted in the study of mental defect as it is in any other area of genetic interest. Dr. Jervis in the third paper of the Symposium will review our present knowledge of the genetics of mental defect, a field in which he has been making significant contributions for some years.

REFERENCES

ADLERSBERG, D., PARETS, A. D., & BOAS, E. P., 1949. Genetics of atherosclerosis. *J. Am. M. Ass.*, 141: 246–254.

BORNSTEIN, J., & LAWRENCE, R. D., 1951. Two types of diabetes mellitus, with and without available plasma insulin. *Brit. M. J.*, 1: 732.

DRAPER, GEO., DUPERTUIS, C. W., & CAUGHEY, J. L., 1944. *Human Constitution in Clinical Medicine.* New York: Paul B. Hoeber, Inc., pp. 273.

GILBERT, J. A. L., 1949. Association of maternal obesity, large babies, and diabetes. *Brit. M. J.*, 1: 702–704.

HANHART, E., 1950. Neue Forschungsergebnisse über die Vererbung des Diabetes mellitus so wie Anhaltspunkte für seine primare Genese in Stammhirn. *Arch. Julius Klaus Stift.*, 25: 586–598.

KRISS, J. P., & FUTCHER, P. H., 1948. The relation between infant birthweight and subsequent development of maternal diabetes mellitus. *J. Clin. Endocr.*, 8: 380–389.

LAWRENCE, R. D., 1951. Types of human diabetes. *Brit. M. J.*, 1: 373–375.

LISTER, J., NASH, J., & LEDINGHAM, U., 1951. Constitution and insulin sensitivity in diabetes mellitus. *Brit. M. J.*, 1: 376–379.

MILLER, H. C., 1945. The effect of the prediabetic state on the survival of the fetus and the birth weight of the newborn infant. *N. E. J. Med.*, 233: 376–378.

MOSS, J. M., & MULHOLLAND, H. B., 1951. Diabetes and pregnancy, with special reference to the prediabetic state. *Ann. Int. M.*, 34: 678–691.

PINCUS, G., & WHITE, P., 1933. On the inheritance of diabetes mellitus. I. An analysis of 675 family histories. *Am. J. M. Sc.*, 186: 1–14.

PINCUS, G., & WHITE, P., 1934. On the inheritance of diabetes mellitus. II. Further analysis of family histories. *Am. J. M. Sc.*, 188: 159–168.

1. The Heredity of Diabetes Mellitus

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(This paper appeared in substance in the June 1952 issue of The American Journal of Human Genetics. Hence it will not be published here. See STEINBERG, ARTHUR G. and WILDER, RUSSELL M. 1952. A study of the genetics of diabetes mellitus. *Am. J. Human Genet.* 4: 113–135.)

2. Genetic Studies on Idiopathic Hypercholesteremia[1]

DAVID ADLERSBERG, LOUIS E. SCHAEFER, STANLEY R. DRACHMAN, AND ARTHUR G. STEINBERG,[2]

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IN the first decade of the present century only four diseases could be classified as inborn errors of metabolism—albinism, alcaptonuria, cystinuria, and pento-

[1] This study was reported (in part) by a research grant from the Division of Research Grants and Fellowships of the National Institutes of Health, United States Public Health Service.

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suria. Since that time many additional diseases of this nature have been recognized, involving protein, carbohydrate and lipid metabolism.

This study deals with the hereditary aspects of errors of cholesterol metabolism, (primary cholesterol lipidosis, or xanthomatosis).

The genetic mechanisms of this disorder have been studied extensively in the past forty years. Opinions as to the mode of transmission vary. Those investigators who used the presence of xanthomata as the criterion for the trait obtained different results from those who considered hypercholesteremia to be the identifying characteristic. Recent studies tend to support the concept that hypercholesteremia rather than xanthomatosis is the principal manifestation of the inherited factor, and that it may be transmitted as an incomplete dominant.

In support of the theory that hypercholesteremia is the key factor rather than xanthomatosis Adlersberg and his associates (9b) studied thirty-five persons with xanthomatosis, all of the family members of these thirty-five individuals who could be contacted, and 29 patients with xanthomatosis whose families were not available for study, a total of 201 persons. The most frequently encountered abnormality was hypercholesteremia (60%) and next in frequency was coronary atherosclerosis (40%). Xanthelasma and corneal arcus followed in frequency (30 and 18% respectively); and tuberous or tendinous xanthoma was the least frequent stigma (12.5%). Thus the sign from which the disorder derives its name was surpassed in frequency by the other stigmata of the disease, particularly hypercholesteremia.[3] Furthermore, in a study of 122 persons under the age of 50 with coronary artery disease, conducted by Boas et al. (9a) a serum cholesterol level above 300 mgm. per 100 ml. was found in 71 (58%); corneal arcus in 22, xanthelasma in 12 and xanthomata in only three.

Because of these and other data indicating that an error in cholesterol metabolism might be considered a common denominator for most patients with early coronary atherosclerosis, and because previous studies of this subject as noted above dealt only with single families (7) or early coronary artery disease (9) we attempted to estimate the incidence of hypercholesteremia in the population of a general hospital (10). Among 200 consecutive admissions to a male and a female ward of The Mount Sinai Hospital in New York City the incidence of hypercholesteremia was found to be 17.3%. An analysis of the families of the hypercholesteremic index patients revealed a high frequency of "hereditary hypercholesteremia" (5.5%). It seemed necessary, therefore, not only to expand this study to a larger group of families, but also to subject the data to a careful genetic and statistical evaluation.

[3] Hypercholesteremia defined as serum cholesterol levels in excess of 299 mg. per 100 ml. by the Bloor method or in excess of 279 mg. per 100 ml. by the Sperry-Schoenheimer method of analysis.

This report summarizes studies of hypercholesteremia in 250 male and 250 female consecutive admissions to The Mount Sinai Hospital, and presents an analysis of the families of 59 of the 75 patients with idiopathic hypercholesteremia. These 500 patients include the sample of 100 males and 100 females previously reported. The detailed data and analysis will be presented elsewhere.

PROCEDURE

On admission a careful personal and family history was obtained. A physical examination was performed with particular attention to the signs and symptoms associated with idiopathic hypercholesteremia (corneal arcus, xanthelasma, xanthoma, and coronary artery disease). The morning after admission a specimen of venous blood was drawn after the patient had fasted for 12 hours. Total serum cholesterol was determined by the Sperry-Schoenheimer method. Values of 280 mgm. per 100 ml. or higher were considered to be hypercholesteremic.

Whenever the history, the physical examination, or the total serum cholesterol of the proband suggested the presence of idiopathic hypercholesteremia, serum cholesterol determinations were performed on all available members of the immediate family.

RESULTS

Ninety-seven of the 500 probands were found to have a serum cholesterol level exceeding 279 mgm. per 100 ml. This group consisted of 41 men and 56 women with an age range of 16 to 80 years, average 52.8 years. The serum cholesterol of these hypercholesteremic patients varied from 280 to 983 mgm., average 348 mgm. per 100 ml. For purposes of more detailed analysis this group was subdivided into: 1) those with a disease commonly associated with hypercholesteremia; 2) those with idiopathic hypercholesteremia whose families could not be surveyed; 3) those with idiopathic hypercholesteremia whose families were surveyed at least in part.

Twenty-two of these 97 patients, 8 men and 14 women, were suffering from diseases commonly associated with hypercholesteremia (Group I). Their ages ranged from 16 to 86 years, average 50.7 years; their serum cholesterol levels varied from 280 to 983 mgm., average 381 mgm. per 100 ml. In these 22 patients there were 14 instances of intra- or extrahepatic obstruction associated with icterus, four instances of nephrosis, and four endocrine disorders (Sheehan's syndrome, Cushing's syndrome, and two with uncontrolled diabetes).

Of the remaining 478 patients, the distributions of the values for the male and female patients are not significantly different ($X^2_{12} = 10.664$, $P = 0.50$). Thirty-two males and 43 females had cholesterol levels of 280 mgm. or greater

corresponding to percentage frequencies of 13.2 and 18.2 respectively. These frequencies are not significantly different ($X_1^2 = 2.077$, $P > 0.10$). The frequency of hypercholesteremia among the 478 patients was 15.7% (75/478 × 100).

The frequency of idiopathic hypercholesteremia while higher than one might have expected is in agreement with the first sample of 200 probands in which hypercholesteremia was found in 17.3%, and this figure may be a minimum value because of the well-known effect of pyrexia, especially of long duration, and of cachexia in lowering the cholesterol level.

A vigorous attempt was made to examine all available (i.e. surviving or living in or close to New York) immediate relatives of the 75 hypercholesteremic patients. No relatives of 16 of these patients, eight men and eight women, could be examined.

The ages of these 16 patients (Group II) varied from 34 to 80 years, average 55.4 years. The total serum cholesterol ranged from 280 to 430 mgm., average 321 mgm. per 100 ml. In all of these patients the possibility of hereditary hypercholesteremia arose, but in no case was further examination possible. This was usually due to the fact that all the family members lived in widely separated areas throughout the country, and sometimes throughout the world. In some cases there was no living family member. Occasionally an uncooperative individual was encountered, who, without any stated reason, objected to being studied. This group emphasizes one of the greatest difficulties in a genetic study of this type; namely, the inability to obtain data on all family members.

Of the remaining 59 hypercholesteremic patients there were 25 males and 34 females. Their ages ranged from 33 to 80 years, average 54.8 years. Their total serum cholesterols ranged from 280 to 432 mgm. average 320 mgm. per 100 ml. Cholesterol determinations were made on a total of 97 sibs and 110 children of these patients. Among these 110 children there was one pair of identical twins; these were counted as a single zygote for purposes of analysis. The frequency of hypercholesteremia among the sibs was 51.5% (50/97 × 100) and among the children 29.4% (32/109 × 100). Both these frequencies are significantly higher than that found among the 478 patients; in each case P is less than 0.001. In contrast to the probands, their sibs and children were essentially healthy persons who were examined on an ambulatory basis.

After this study was nearly completed Keys et al. (11) published serum cholesterol values which are expected to be exceeded by only 5% of the population in each 5 year age group. When these values are used to define hypercholesteremia in the present sample, one finds 10.7% of the males (24/225 × 100) and 13.4% of the females (29/216 × 100) hypercholesteremic. Again it is evident that the frequencies of hypercholesteremia among the male and female patients are not significantly different. Patients of less than 18 years of

age or over 77 years of age are omitted because Keys et al. did not publish figures for these age groups. The frequency of hypercholesteremia for the total usable sample is 12.0%. The frequency of hypercholesteremia among the sibs of these "hypercholesteremic" probands is 36.2% (29/78 × 100), and among the children 34.0% (16/46 × 100).

These frequencies are significantly greater than those found for the index patients. This finding is in agreement with our previous observations.

It should be stressed that insofar as the values published by Keys et al. are applicable to our data only 5% of the sibs and children of the patients would be expected to have elevated cholesterol levels, rather than the 36.2% and 34.0% respectively, observed to have such elevated levels. This is merely another way of emphasizing the significant increase in the frequency of hypercholesteremia found among the sibs and children of the probands.

Our sample of 478 index patients was composed of 266 Jews (55.6%) and 212 non-Jews (44.4%). It may be stated that the Jewish and non-Jewish population of the Hospital presented various degrees of heterogeneity. The majority of the Jewish patients was of East European origin (Russia and Poland) while a minority was of West European origin (Germany, Holland and Belgium). The non-Jewish population consisted of persons of Italian, Irish, English and Slavic origin; a considerable number were Puerto Ricans and approximately one-quarter were non-white.

Two questions arise in relation to the ethnic origin of the patients: (1) is idiopathic hypercholesteremia equally frequent among the Jewish and non-Jewish groups of patients? (2) is the frequency of hypercholesteremia among the sibs and children respectively of the hypercholesteremia probands of these two groups the same?

When the material is analysed from this standpoint it shows that hypercholesteremia is more frequent among the Jewish probands (21% vs. 9%) and that the frequency of hypercholesteremia among the sibs and children of the hypercholesteremic probands is not dependent upon the patient's religion or ethnic group, since it occurred with approximately the same frequency among the sibs and children of the non-Jewish hypercholesteremic probands as compared with the Jewish (45.4% and 28.5% for the sibs and children of the non-Jews vs. 52.3% and 29.6% for those of the Jews).

DISCUSSION

The question arises as to whether the increased frequency of hypercholesteremia among the sibs and children of patients with hypercholesteremia is genetically determined. It must be stated at once that the present data do not permit a conclusive answer because the familial analyses are incomplete. The number of families in which both parents could be investigated or in which the proband's spouse could be tested is too small. Furthermore, a satisfactory

estimate of the frequency of hypercholesteremia in the population at large is not available at present. Studies designed to supply the necessary data for genetic and population analyses are now in progress.

At the present time it may be stated, however, that the frequency of hypercholesteremia among the sibs and children of the index patients by either of the criteria used is too high to permit an assumption of a recessive gene as the causal factor if genetic determination is involved. The assumption of a dominant gene with complete penetrance requires that somewhat more than 50% of the sibs and children be hypercholesteremic. The excess over 50% expected for the sibs cannot be determined without knowing the condition of both parents, and similarly it cannot be determined for the children without knowing the status of the index patients' marital partners, or alternately without knowing the frequency of the gene in the population.

The sibs show a frequency of hypercholesteremia slightly in excess of 50% when hypercholesteremia is equated to serum cholesterol levels of at least 280 mgm. per 100 ml. The children do not approach 50% by this standard, nor by the one based on the data of Keys et al. Consequently a dominant gene showing complete penetrance seems unlikely. Another requirement for a dominant gene is that the frequency of hypercholesteremia be the same among the sibs and children of the index patients. This condition is not realized when levels of at least 280 mgm. per 100 ml. are used to define hypercholesteremia, but is realized within statistical limits when the more accurate procedure employing the standards of Keys et al. which takes age variations into account is used. As a working hypothesis, then, it may be assumed that hypercholesteremia in the families of hypercholesteremic probands is determined by a dominant gene with incomplete penetrance. It must be stated, however, that the mode of inheritance is unknown at present, and remains to be worked out.

A comparison of the present study with previous observations is of interest. The results of the study of patients with familial xanthomatosis also supported the concept that this syndrome is inherited as a dominant trait with incomplete penetrance, and that hypercholesteremia rather than xanthomatosis is the principal manifestation of the inherited factor (9b). Similarly the studies of Wilkinson et al. presented evidence that hypercholesteremia is transmitted as an incomplete dominant trait in the clan studied by them. Stecher and Hersh (12) concluded from their genetic analysis of the data of Boas, Parets and Adlersberg (9a) on hypercholesteremia among the siblings of patients with coronary artery disease under age 50, that the hypercholesteremia was transmitted via a dominant gene with incomplete penetrance. Thus the present working hypothesis is in agreement with previous observations concerning the mode of transmission of hypercholesteremia.

The finding that hypercholesteremia is as frequent among the sibs and children respectively of Jewish and non-Jewish hypercholesteremic index patients

may perhaps indicate that environmental factors such as different occupations, housing and dietary patterns are not of decisive importance in determining the presence or absence of hypercholesteremia. Such a conclusion would lend support to the concept that hypercholesteremia is primarily genetically determined and that the gene leading to a disturbance of lipid metabolism which manifests itself as hypercholesteremia is more frequent among Jews than among non-Jews. It may be recalled that other disturbances of lipid metabolism such as Niemann-Pick disease (sphingomyelin lipidosis) and Gaucher's disease (cerebroside lipidoses) also occur more frequently among Jews (1, 8b).

The validity of these tentative conclusions awaits the extension of this study to a more representative and complete population group. However, even these preliminary observations shed some light on the complicated error of metabolism involved in idiopathic hypercholesteremia and the predisposition to early atherosclerosis.

REFERENCES

1. Adlersberg, D. 1951. Hypercholesteremia with predisposition to atherosclerosis: an inborn error of lipid metabolism. *Am. J. Med.*, 11: 600.
2. (a) Steiner, A., & Domanski, B. 1943. Serum cholesterol levels in coronary arteriosclerosis. *Arch. Int. M.*, 71: 397. (b) Morrison, L. M., Hall, L., & Cheyney, M. L. 1948. Cholesterol metabolism. Blood serum cholesterol and ester levels in 200 cases of acute coronary thrombosis. *Am. J. M. Sc.*, 216: 32. (c) Gubner, R. & Ungerleider, H. E. 1949. Arteriosclerosis: A statement of the problem. *Am. J. Med.*, 6: 60.
3. (a) Gertler, N. M., Garn, S. M.; & Lerman, J. 1950. The interrelationship of serum cholesterol, cholesterol esters, and phospholipids in health and in coronary artery disease. *Circulation* 2: 205. (b) Gertler, N. M. & Garn, S. M. 1950. Lipid interrelationship in health and coronary artery disease. *Science* 112:14. (c) Kellner, A., Correll, J. W. & Ladd, A. T. 1951. The influence of intravenously administered surface-active agents on the development of experimental atherosclerosis in rabbits. *J. Exp. M.*, 93: 385.
4. Duff, G. L., & Payne, T. F. B. 1950. The effect of alloxan diabetes on experimental cholesterol atherosclerosis in the rabbit. III. *J. Exp. M.*, 92: 299.
5. (a) Gofman, J. W. et al. 1950. Blood lipids and human atherosclerosis, *Circulation*, 2: 161. (b) Jones, H. B., Gofman, J. W. et al. 1951. Lipoproteins in atherosclerosis, *Am. J. M.*, 11: 358. (c) Keys, A. 1951. Cholesterol, "Giant molecules" and atherosclerosis. *J. Am. M. Ass.*, 147: 1514. (d) Keys, A. 1951. "Giant molecules" and cholesterol in relation to atherosclerosis. *Bull. Johns Hopkins Hosp.*, 88: 473. (e) Review. 1951. Atherosclerosis, serum cholesterol, and lipoproteins, *Nutr. Rev.*, 9: 167.
6. Gould, R. G. 1951. Lipid metabolism and atherosclerosis. *Am. J. M.*, 11: 209.
7. (a) Lane, G. C. & Goodman, J., Jr. 1935. Xanthoma tuberosum. *Arch. Derm. Syph.* Chic., 32: 377. (b) Sperry, W. M. & Schick, B. 1936. Essential xanthomatosis: Treatment with cholesterol-free diet in two cases. *Am. J. Dis. Child.*, 51: 1372. (c) Muller, C. 1938. Xanthomata, hypercholesteremia, angina pectoris. *Acta med. scand.*, Supplement 89: 75. (d) Bloom, D., Kaufman, S. R. & Stevens, R. A. 1948. Hereditary xanthomatosis. *Arch. Derm. Syph.* Chic., 45: 1.
8. (a) Thannhauser, L. J. & Magendantz, H. 1938. The different clinical groups of xan-

thomatous diseases. *Ann. Int. M.*, 11: 1662. (b) THANNHAUSER, L. J. 1950. Lipidoses: Diseases of cellular lipid metabolism, *Oxford University Press*, 131: 139.

9. (a) BOAS, E. P., PARETS, A. D. & ADLERSBERG, D. 1948. Hereditary disturbance of cholesterol metabolism: A factor in the genesis of atherosclerosis. *Amer. Heart J.*, 35: 611. (b) ADLERSBERG, D., PARETS, A. D. & BOAS, E. P. 1949. Genetics of atherosclerosis: Studies of families with xanthoma and unselected patients with coronary artery disease under the age of fifty years. *J. Am. M. Ass.*, 141: 246.
10. ADLERSBERG, D., SCHAEFER, L. E., & DRACHMAN, S. R. 1952. The incidence of hereditary hypercholesteremia. *J. Laborat. Clin. M.*, 39: 237.
11. (a) KEYS, A., MICKELSEN, O., MILLER, E. V. O., HAYES, E. R. & TODD, R. L. 1950. The concentration of cholesterol in the blood serum of normal man and its relation to age. *J. Clin. Invest.*, 29: 1347. (b) KORNERUP, V. 1950. Concentration of cholesterol, total fat, and phospholipid in serum of normal men. *Arch. Int. M.*, 85: 396.
12. STECHER, R. M. & HERSH, A. H. 1949. Note on the genetics of hypercholesteremia. *Science*, 109: 61.
13. WILKINSON, C. F., JR., HAND, E. A., & FLIEGELMAN, M. T. 1948. Essential familial hypercholesterolemia. *Ann. Int. Med.*, 29: 676.

3. Genetic Factors in Mental Deficiency

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DURING the past fifty years many changes have occurred in the evaluation of the influence of heredity on mental deficiency, from the emphasis on purely genetic factors which characterizes the studies of the "Kallikak" and "Jukes" families (1) to the sociological investigations of Davies (2) and others, which minimize the role of heredity in mental deficiency. No agreement has been reached; in fact, contradictory and confused statements may still be found in some current and authoritative literature, and figures as widely apart as 10% and 80% may be encountered as representative percentages of defective individuals due to genetic mechanisms.

It is not the purpose of this presentation to outline the history of the problem nor is there any claim being made to new original developments and to exhaustive treatment of the many questions involved. Rather, as the character of the symposium indicates, this is a brief review of present day concepts and attitudes on the problem, with a summary of some available data. The material is seen mainly from the point of view of the clinician whose chief interest is the application of scientific data to practical genetic counseling in the attempt to limit the number of defective individuals.

Perhaps the greatest difficulty in assessing much of published work is due to the fact that many investigators have assumed that mental deficiency is an entity or, even, an etiologic unit. This assumption is obviously erroneous and contrary to modern trends in the study of mental deficiency. It is widely ac-

cepted today that the term mental defect should be maintained only as a convenient classification used mostly for administrative purposes. The term, in fact, denotes only a symptom which is the common denominator to an heterogeneous group of conditions each characterized by its own etiological factors, clinical manifestations and pathological lesions. Consequently, every effort is directed today toward a fuller characterization of each single condition by means of precise clinical and laboratory procedures. Once the condition is thus delimited and isolated, direct genetic methods can be usefully applied, i.e., pedigree studies, calculation of ratios of affected to unaffected individuals, estimation of gene frequencies, measurement of parental consanguinity, ascertainment of mutation rates, variations in age of onset and severity, etc.

The data thus obtained may be reviewed by giving, first, some examples of action of single dominant and recessive genes and, second, by discussing briefly the importance of the multifactorial (polygenic) theory of inheritance in the study of mental deficiency.

As an example of dominant condition, tubero-sclerosis may be quoted. This is a peculiar type of mental defect characterized by the presence of cutaneous lesions (adenoma sebaceum), tumors in different organs (rhabdomyoma of the heart, hamartoma of kidneys, phakomata of the retina, etc.), epilepsy, and occasionally, bone changes. Lesions of the brain are highly characteristic both grossly and microscopically. In about a third or less of the cases, examination of the family history shows the presence of a similar condition in sibs, parents and other relatives, the pedigree being consistent with the hypothesis of a single dominant autosomal gene. Thus, cases have been traced through 5, 4 and 3 generations (3). The well-known clinical observation of the frequency of incomplete forms ("formes frustes") in tubero-sclerosis is of considerable significance to the genetic study of the disease. In fact, complete forms are rarer than incomplete ones. The latter includes cerebral forms without skin manifestations and with or without visceral tumors; cerebral forms without mental deficiency but with epilepsy; monosymptomatic forms with only one manifestation such as rhabdomyoma of the heart, and all the possible combinations of one, two or more manifestations (4). Because of the extreme variability of the clinical symptomatology, it is difficult to recognize a certain number of patients. Consequently, any evaluation of family data is to be taken with caution. In addition to the variations in expressivity, the study of families would suggest that in certain instances penetrance may be reduced.

Sporadic cases may be accounted for by mutation. Gunther and Penrose (5) have estimated the mutation rate at about 1 in 120,000 per individual per generation on the hypothesis that 75% of the cases are transmitted, and 25% are the result of new mutation, assuming the incidence of the disease at about 1 in 30,000. It should be added that several cases of tubero-sclerosis have been published suggesting the possibility of recessive mechanisms (6). For instance,

in a family of personal observation in which only two sibs were affected out of seven, a close consanguinity was present: the parents of the patients were second cousins and the four grandparents were first cousins on both sides since all four were the offspring of two sisters.

Tubero-sclerosis, in itself a rare condition, is one of a group of mental retardations characterized by cutaneous lesions and called, therefore, "dermodysplastic" mental deficiencies. Among other conditions of this group one may mention neurofibromatosis (Recklinghausen's disease) which is characterized by mutiple skin pigmentations, neurofibromata and bone changes. Mental defect is not always present. Pedigrees are available (3) showing an irregular type of dominance quite similar to those seen in tubero-sclerosis and consistent with the hypothesis of a dominant gene with varying expressivity and, at times low penetrance. Here again formes frustes are common and monosymptomatic forms are not rare.

"Naevoid" mental defect or Sturge-Weber's disease, a condition characterized by angioma of the face and calcification of cortical regions of the brain with epilepsy and mental deficiency (7), belongs in the same group of diseases and familial cases have been reported suggesting an irregular dominant heredity. The presence of often unrecognized abortive forms in relatives of patients may account for the incompleteness of many pedigrees. Somewhat similar is the condition described by Hippel and Lindau in two or more generations and characterized by naevi of the cerebellum, retina and other organs (8). The occurrence of sporadic forms may be explained either by mutation or by the incompleteness of investigation owing to abortive forms.

Darrier's disease, or follicular dyskeratosis, a well known skin disease, is often accompanied by mental defect (9). Familial occurrence is observed in about a third of the cases and the evidence suggests irregular dominance.

In other "dermodysplastic" forms of mental deficiency the evidence is too scanty to permit genetic generalization. Albright's disease, a condition in which pigmentation of the skin is accompanied by fibroplastic bone lesions, is sometimes associated with mental deficiency and occurs occasionally in families; the disease in some respects is not unlike tubero-sclerosis (10). Xerodermic idiocy in which mental defect coexists with hyperkeratosic lesions of the skin has been observed in sibs (11), but whether the condition is dominant or recessive is not known.

Closely related in their genetic behavior to "dermodysplastic" forms of mental deficiency are the "dysostotic" forms characterized by mental impairment accompanied by lesions of the osseous system. The most important are the cranio-facial dysostoses, in which mental defect is associated with cranial anomalies. Acrocephaly in which the vertical diameter of the skull is abnormally high is a deformity common to various syndromes probably closely interrelated. In the Crouzon syndrome (12) acrocephaly is associated with exoph-

thalmos, abnormally small orbital cavities, narrow optic foramina and, not always, increased intracranial pressure. That cases may be observed in various generations is well known and recently Flippen (13) published a pedigree of a family in which affected members were found in three generations suggesting in this family the action of an autosomal dominant gene with complete penetrance. In other pedigrees, penetrance appears to be lower. As for expressivity of the gene, it is a common clinical observation that wide variations exist in the degree of skull deformity and exophthalmos. In the Apert syndrome (14), acrocephaly is accompanied by exophthalmos, hypertelorism, and syndatcylia. Occasionally, a dominant heredity can be suspected from pedigree studies such as that published by Mohr (15). Crouzon's and Apert's syndromes may be present in the same family suggesting that the two diseases are genetically identical. In the Greig syndrome hypertelorism, i.e., abnormally increased intrapupillary diameter, is the outstanding deformity. Here also some evidence has been brought forward suggesting in some families a dominant inheritance (16).

Less common are dysostotic forms involving extremities. Arachnodactyly (Marfan's syndrome), characterized by long limbs and "spidery" hands and feet, has been repeatedly described in various members of a family. Clinical manifestations are multiple including numerous skeletal abnormalities, ocular anomalies (coloboma and dislocation of the lenses) and cardiac defects. Mental deficiency is common. "Formes frustes" and monosymptomatic forms have been reported. Expressivity varies considerably and penetrance in certain families seems low but the hypothesis of a dominant gene would appear to be consistent with pedigree data (17). The extremities are also involved in achondroplasia, a condition of arrested ossification of the cartilage with resulting shortness of the long bones. Other bone changes are often present (large head, sunken nose, high palate, spine deformities). Wide variations exist in the degree of involvement of the skeleton and the number of bones affected. Mild forms are not infrequent and may remain undiagnosed. Although mental defect is not the rule, a certain degree of mental impairment is often present, no correlation existing between degree of skeletal involvement and intellectual development. From the extensive studies of Mörch (18), it is apparent that the disease behaves as a dominant character. Of considerable interest is the pedigree published by Stephens (19) describing three generations from an achondroplastic man; there were 40 descendants showing the defect and 52 normal. It should be noted that this complete expressivity and high penetrance of the gene is not the rule in the disease.

It is difficult to estimate the number of defectives determined by these dominant genes since the main features of the whole group seem to be the wide variation of clinical manifestations and the presence of minimal, often unrecognizable "formes frustes." However, their percentage is probably not

above 1–2 of all defectives. One can confidently expect that this figure will significantly increase with the refinement of our diagnostic methods.

The study of recessive genes in the causation of mental defect is more advanced than that of dominant heredity. Types of defect due to recessivity are more sharply segregated and perhaps more easily identifiable from a clinical point of view since "formes frustes" are the exception rather than the rule. Moreover, in many if not in all recessive mental deficiencies, metabolic alterations are present and exact methods of biochemical research can be successfully applied to the study of the condition.

In these types of recessive mental deficiencies associated with biochemical alterations several groups may be identified, according to the class of substances involved in the metabolic disorder.

The first group includes the types of mental deficiency associated with disorders of metabolism of lipids, the so-called cerebral lipidoses, i.e., the various forms of amaurotic idiocy, gargoylism and the rare Nieman-Pick and Gaucher's diseases. Each form possesses a common clinical trait, mental defect, but distinctive clinical features. Congenital amaurotic idiocy is present at birth and appears to be rapidly fatal (20). Infantile amaurotic idiocy (Tay-Sachs' disease) begins at about 6 months of age, is characterized by rapid mental deterioration, blindness and motor impairment. Death occurs usually before the third year of age (21). The late infantile form of amaurotic idiocy (Bielschowsky's disease), is somewhat late in onset (between the second and third year) and the course is somewhat more protracted than in the infantile form (22). Juvenile amaurotic idiocy (Spielmeyer-Vogt's disease) shows slow progressive mental deterioration extending from the age of 5–6 years to the age of 16–18 years when death usually occurs; there are blindness and pigmentary degeneration of the retina (23). Late amaurotic idiocy (Kufs' disease) begins after adolescence, the progression is slow extending over a period of 10–20 years, terminal profound dementia is observed (24). Gargoylism is characterized by mental defect, dystrophic changes of bone and enlargement of liver and spleen (25). Nieman-Pick's disease is similar in its mental manifestations to Tay-Sachs' disease but there is in addition conspicuous hepatosplenomegaly (26). The rare infantile form of Gaucher's disease shows a rapid, fatal course, idiocy and various neurological changes in addition to enlargement of spleen and liver (27).

Familial occurence is highly characteristic of all forms of cerebral lipidosis, parents are usually normal and the rate of parental consanguinity is higher than in the population at large. Statistical analyses of affected to normal sibs have been made in three of the less rare forms, i.e., infantile amaurotic idiocy (28), juvenile amaurotic idiocy (29), and gargoylism (25). The data are consistent with the hypothesis of a single autosomal recessive gene.

A second group of recessive diseases consists of types of mental deficiency associated with abnormalities in the metabolism of amino acids. The most

important is phenylpyruvic oligophrenia or phenylketonuria (Fölling's disease) (30). Clinically, the disease is characterized by inborn mental defect, usually severe in degree, not infrequently accompanied by epileptic attacks and occasionally by psychotic episodes (31). Biochemically, the condition is characterized by urinary excretion of phenylpyruvic acid, phenylalanine, phenylacetic and phenyllactic acid (32). In the blood phenylalanine is present in abnormally high amounts, from 20 to 30 times its normal quantity (33).

The genetics of phenylpyruvic idiocy has been the object of several investigations indicating beyond reasonable doubt that the condition is recessive. In fact, the ratio of affected to normal sibs, the high percentage of consanguineous marriage among parents of patients, and the distribution of the disease among relatives indicate that a single autosomal gene is responsible for the condition (34, 35, 30).

Another disease in which mental defect is accompanied by disorderly amino-acid metabolism is Wilson's disease. Degeneration of the basal ganglia of the brain and cirrhosis of the liver are the characteristic pathological features. Abnormally high urinary excretion of amino acids with consequent depletion of amino nitrogen are the biochemical abnormalities. Recessive inheritance seems well established (36).

A third group consists of types of mental defect associated with aberrant metabolism of carbohydrates. Two conditions may be mentioned, galactosuria and glycogenosis. Galactosuria occurs only in infants and is characterized by the fact that galactose is not metabolized normally and accumulates in the body fluids (37). As in other metabolic errors of sugars, the mode of inheritance is apparently recessive. Glycogenosis is a condition characterized by failure in the mechanism of breaking down of glycogen with consequent storage of the carbohydrate in certain organs. Various forms are recognized (hepatic, cardiac, gastric, muscular forms) depending upon the localization of the glycogen deposit. The central nervous system may be among the organs involved, producing mental defect (38).

A fourth group of recessive mental deficiencies associated with alteration of metabolism of pigments within the central nervous system is represented mainly by Hallervorden-Spatz disease (39). Clinically, the outstanding manifestation is a slowly progressive muscular rigidity, extrapyramidal in type, extending over a period of several years and accompanied by mental deterioration. Pathologically, there is a gross accumulation of pigment in the globus pallidus and substantia nigra. The disease occurs often in sibs.

In all these recessive mental deficiencies a faulty enzymatic mechanism is probably at the basis of the chemical abnormality. It is tempting to attribute the common genetic behavior to a genetically determined lack of a specific normal enzyme responsible for the faulty metabolic step. In each disease, then, a gene change would determine the absence of an enzyme and as a consequence

there would be a failure in the corresponding step in the chain of normal enzymatic reactions. This hypothesis follows the classical conception of Garrod (40) and new support for it is found in the recent work on the genetics of microorganisms (41) indicating a one to one qualitative relation between units of inheritance, the genes, and units of biochemical activity, the enzymes. It may be an adequate explanation for some types here described such as phenylpyruvic idiocy in which the defective hydroxylation of phenylalanine might well be the failure of a normal enzymatic reaction genetically controlled. However, it would be difficult to explain in this simple manner other types such as some lipidoses in which an abnormal metabolite accumulates in the nerve cells.

Although the metabolic abnormalities involved are only imperfectly known, other probable recessive forms of mental defect may be placed in this group; among these are certain forms of diffuse sclerosis of the brain such as the Krabbe (42) and the Scholz' types (43), in which a biochemical alteration of the myelin is present, often on a familial basis; and the recessive types of muscular dystrophy (44) accompanied not rarely by intellectual defect. In other recessive conditions, metabolic alterations can only be suspected. One may mention, for instance, some forms of severe mental defect characterized by degeneration of the molecular layer of the cerebellum (45). Friedreich's ataxia, also a cerebellar degeneration, often accompanied by mental defect, behaves as a Mendelian recessive (46).

That recessive mechanisms are responsible for other still unrecognized types of mental deficiency seems certain. It is interesting in this respect to quote the findings of two exemplary genetic studies in isolated communities. Sjögren (47), in a northern Swedish community in which inbreeding was remarkably high, found 52 defectives in 34 families, the data being consistent with the hypothesis of an autosomal single recessive gene. Ruepp (48), in a Swiss village of some 400 people in which there was also a high degree of inbreeding, found 62 defectives whose genetic patterns were clearly recessive. Both investigators found no distinctive clinical manifestations besides mental defect in the defective individuals studied. It is reasonable to assume, however, that the patients belong to some still unrecognized clinical grouping.

It is pertinent at this point to mention briefly the problem of mongolism, a disease easily identifiable even by laymen. The modern tendency apparently is in favor of attributing the disease to maternal environmental factors with exclusion of any genetic hypothesis (49). However, no conclusive evidence against a genetic mechanism can be derived from observational data. Twin studies, for instance, indicating the complete absence of discordant identical pairs, the rarity of concordant not identical twins and the frequency of discordant not identical pairs is more consistent with the endogenous than the exogenous theory (50). Moreover, there is a slight increased incidence of the disease among sibs (51) and the well-known increased frequency of abortions

in mothers of mongoloids would suggest that familial occurrence of the disease is higher than usually observed, some of these aborted fetuses being possibly mongoloid individuals. Finally, the extraordinary physical likeness of mongoloids would be more in keeping with an endogenous genetically determined condition than with the action of exogenous variable factors. To be sure, the problem is of considerable practical interest owing to the high incidence of the disease (almost 0.2% of all newborn children). The recent hypothesis of Penrose (52) deserves, therefore, attention. According to this authority, susceptibility to mongolism would be a simple homozygous recessive trait with a gene frequency as high as 1 in 5 but a pentrance as low as 1 in 27. This would bring the incidence of mongolism to the observed figure of about 1 in 600 births. Factors determined by maternal age control the expression of the trait. The action of these factors is considerably reduced when the mother is herself homozygous for the gene and, therefore, potentially, although not actually, a mongol.

Concerning sex-linked genes, the theory advanced by Rosanoff et al (53) and by Brugger (54) that sex-linked types of heredity are of considerable significance in the etiology of mental defect has found little support in recent studies. To be sure, an occasional pedigree of severe mental deficiency suggesting the action of sex-linked genes has been reported (55, 56). Moreover, certain cases of microphthalmia associated with mental deficiency, a condition easily detected, appear to behave as sex-linked (57) or partially sex-linked conditions (58). However, simple recessive forms have been reported (59). Partial sex linkage in spastic paraplegia, a condition accompanied by mental defect, has been suggested by Haldane (60) but it is doubtful that the clinical material is homogeneous.

It may be seen from this incomplete review that the range of mental deficiencies due to dominant or recessive genes is large although, if one excepts mongolism, the number of cases in each type is not conspicuous. It is reasonable to assume that the range of types will become larger and the number of cases greater with the improvement of diagnostic procedures. However, once cases due to major genes are properly identified, there will remain probably a residual number of defectives which cannot be accounted for only by environmental influences. There is reason to believe that these individuals will show no clinical manifestations besides intellectual impairment, belonging to the "undifferentiated" or "aclinical" group. That this group is large is an accepted fact but how large is still unknown. Estimates vary from 20 to 80 per cent of all defectives. In fact, no reliable data on its incidence are available since satisfactory criteria for recognizing the undifferentiated defective are still lacking. It is a matter of common observation that a certain number of patients are tentatively classified in the undifferentiated group only because of insufficient anamnestic data or incomplete clinical observation. Further refinement of

diagnostic methods and better understanding of etiological factors in the single patient will certainly help in a clearer identification and definition of the undifferentiated defective.

Lack of satisfactory diagnostic criteria and unreliable data on incidence are sufficient to explain the difficulties encountered in the evaluation of the significance of genetic factors in the etiology of the undifferentiated defective. It may be of help in the solution of this problem to fall back on some old concepts now almost universally accepted concerning the distribution of intelligence in the general population. It is fairly well established that the distribution curve of intelligence approximates the Gaussian curve. Moreover, when in a cross section of the population, one tests random samples of high grade defectives, who presumably are mostly of the undifferentiated type, the sample yields a distribution which does not differ significantly from the Gaussian curve (61). It seems, therefore, that the undifferentiated defectives represent merely that group of individuals on the curve which lies in the range below the arbitrary line indicating I.Q. 70. They are an integral part of the general population just as much as individuals of superior intelligence with an I.Q. above 130. From the form of the curve, it is evident that the largest number of these defectives will be in the moron classification and a very small number at the low level of intelligence. It is well known, in fact, that the undifferentiated are mostly high grade defectives whereas the low grades belong mostly to clinical types, either exogenous or genetic in etiology. If the undifferentiated defectives are part of the distribution curve of intelligence, one may then assume that the etiological determinants are of the same order as those responsible for variation of intelligence in the general population. The etiological problem of this type of mental deficiency is thus more clearly delimited although, admittedly, still fraught with great difficulties concerning the meaning of the term intelligence and the close interplay of environmental and genetic factors in its determination.

It is generally admitted that in dealing with a graded biological character such as intelligence, displaying continuous variations, it would be extremely difficult to ascribe it to the action of individual major genes. A multifactorial, polygenic theory explains more adequately the observed facts. Accordingly, in the determination of intelligence and, therefore, in the etiology of the undifferentiated defective, one may assume that groups of allelomorphic pairs of genes play a role. Each gene produces a small effect in relation to the total variation of intelligence but their combined effects are additive (or subtractive) and the development in one or the other direction is influenced by the whole group of small genes. Pickford (62) has recently advanced the ingenious theory that as few as 10 pairs of genes acting additively (or subtractively) are sufficient to adequately duplicate the intelligence distribution curve observed in the general population.

There is reason to assume, therefore, that genetic factors are of considerable

importance in the causation of the undifferentiated defective. Additional evidence is offered by the application of correlation techniques between relatives of presumably undifferentiated defectives. Although the diagnosis of undifferentiated deficiency may be open to doubt, some figures can be quoted as significant in this respect: in Denmark, Wildenskov (63) found 51% defectives among sibs of high grade defectives (presumably of the undifferentiated type); Penrose (64) in England 24%; Halperin (65) in America 28%; Roberts (61) in a similar group found a sib-sib correlation of 0.53. Such correlations which are similar to those observed with other graded characters, suggest the action of multiple genes although, of course, do not rule out entirely the influence of environmental factors.

Finally, the data on presumably undifferentiated defective twins indicating a much higher correlation between monozygotic than dizygotic pairs (66) apparently corroborate the importance of genetic factors, provided the data are accepted with the well known reservations common to all twin studies.

In conclusion, from the data presented it would appear that considerable advances have been made in the genetical investigation of mental deficiencies. The role of dominant and recessive genes in several types of mental defect has been established and the important problem of genetical factors in the determination of the undifferentiated defective has been to a certain extent clarified.

The path for future advances lies in the close cooperation between medicine and genetics. It is the task of the medical investigator to single out new entities from the mass of defective individuals by means of clinical, pathological and biochemical studies. There is reason to believe that in the not too distant future, almost every mental defective will be classified in the proper etiological group. Only then will it be possible to assess the relative significance of environmental and genetic factors with any degree of certainty. Genetic counseling in mental deficiency only then will rest on a thorough scientific foundation.

REFERENCES

1. Goddard, H. H. 1912. *The Kallikak Family.* New York: MacMillan.
2. Davies, S. P. 1930. *Social Control of the Mentally Deficient.* New York: Thomas Y. Crowell.
3. Borberg, A. 1951. *Clinical and Genetic Investigations into Tuberosclerosis and Neurofibromatosis.* Copenhagen: Munksgaard.
4. Critchley, M. & Earl, C. B. 1932. *Brain*, 35: 311.
5. Gunther, M. & Penrose, L. S. 1935. *J. Genet.* Cambr. 31: 413.
6. Vaas, J. 1940. *Arch. f. Psych.*, 111: 547.
7. Lamande, A. M. 1948. *La neuroangiomatose encephalo-faciale.* Paris: Masson.
8. Craig, W. M., Wagner, M. P. & Kernohan, J. W. 1941. *Arch. of Neur.*, 46: 36.
9. Cockayne, E. A. 1933. *Inherited Abnormalities of the Skin.* Oxford: Med. Press.
10. Jervis, G. A. 1951. *Arch. Path.* Chic. 51: 640.
11. Ruud, E. 1929. *Hosp. Tid.* 72: 426.
12. Gunther, H. 1933. *Endokrinologie*, 13: 255.

13. Flippen, J. H. 1950. *Pediatrics*, 5: 90.
14. Apert, E. 1906. *Bull. et Mem. Soc. Med. des Hôp.*, 23: 1310.
15. Mohr, O. L. 1939. *Hereditas*, 25: 193.
16. Grieg, D. M. 1926. *Edinb. M. J.*, 31: 260.
17. Rados, A. 1942. *Arch. Ophth.* Chic., 27: 477.
18. Morch, E. T. 1940. *J. Hered.*, 31: 439.
19. Stephens, F. E. 1943. *J. Hered.*, 34: 229.
20. Norman, R. M. & Wood, N. 1941. *J. Neurol.*, 4: 175.
21. Globus, J. 1942. N. Y. *Mount Sinai Hosp. Bull.*, 9: 451.
22. Jervis, G. A. 1940. *Am. J. Dis. Child.*, 60: 88.
23. ——— 1941. *Am. J. Dis. Child.*, 61: 327.
24. ——— 1950. *Am. J. Psychiat.*, 107: 409.
25. ——— 1950. *Arch. Neur. and Psychiat.*, 63: 681.
26. Bauman, T., Klenk, E. & Scheidegger, S. 1936. *Erg. allg. Path.*, 30: 183.
27. Schairer, E. 1948. *Virchovs Arch.*, 315: 395.
28. Slome, D. 1933. *J. Genet.*, Cambr., 27: 363.
29. Sjögren, T. 1931. *Hereditas*, 14: 197.
30. Følling, A., Mohr, O. L. & Ruud, L. 1945. *Oligophrenia phenylpyruvica*, Oslo.
31. Jervis, G. A. 1937. *Arch. Neur. Psychiat.*, 38: 944.
32. ——— 1950. *Proc. Soc. Exp. Biol.* N. Y., 75: 83.
33. Borek, E., Jervis, G. A. & Waelsch, H. 1950. *Proc. Soc. Exp. Biol.* N. Y., 75: 86.
34. Jervis, G. A. 1939. *J. Ment. Sc.*, 85: 719.
35. Munro, T. A. 1947. *Ann. Eugen.*, Camb., 14: 60.
36. van Bogaert, L. & Andre, M. J. 1950. *Encephale*, 39: 1.
37. Bruck, E. & Rapaport, S. 1945. *Am. J. Dis. Child.*, 70: 267.
38. Gunther, R. 1939. *Virchovs Arch.*, 304: 87.
39. Jervis, G. A. 1952. *J. Neuropath.*, 11: 4.
40. Garrod, A. E. 1923. *Inborn Errors of Metabolism.* London: Oxford University Press.
41. Beadle, G. W. 1945. *Chem. Rev.*, Balt., 37: 15.
42. Jervis, G. A. 1942. *Am. J. Dis. Child.*, 64: 1055.
43. Einarson, L. & Neel, A. V. 1944. *Acta Jutlandica*, 16: 1.
44. Bell, J. 1943. *Treas. Human Inher.*, 4: 283.
45. Jervis, G. A. 1950. *J. Nerv. and Ment. Dis.*, 111: 398.
46. Sjögren, T. 1943. *Acta psychiat. et neur.* Suppl., 27.
47. ——— 1932. *Acta psychiat. et neur.* Suppl., 2.
48. Ruepp, G. 1935. *Arch. J. Klaus Stift.*, 10: 193.
49. Benda, C. 1949. *Mongolism and Cretinism.* New York: Grune and Stratton.
50. Jervis, G. A. 1943. *Am. J. Ment. Defic.*, 47: 364.
51. Böök, J. A. & Reed, S. C. 1950. *J. Am. M. Ass.*, 143: 730.
52. Penrose, L. S. 1951. *J. Ment. Sc.*, 97: 738.
53. Rosanoff, A. J., Handy, L. M. & Plesset, I. S. 1937. *Psychol. Monogr.*, 48: 4.
54. Brugger, C. 1942. *Ann. Med. Psychol.*, 100: 313.
55. Martin, J. P. & Bell, J. 1943. *J. of Neur. Psychiat.* London, 6: 154.
56. Herndon, A. W. 1944. *Am. J. Ment. Defic.*, 48: 325.
57. Roberts, J. A. F. 1947. *Brit. Med. J.*, 2: 1213.
58. Sjögren, T. & Lasson, T. 1949. *Acta Psychiat. et Neur.*, Suppl., 56.
59. Kallman, F. J., Barrera, S. E. & Metzger, H. 1940. *Am. J. Ment. Defic.*, 45: 25.
60. Haldane, J. B. S. 1941. *J. Genet.*, 41: 141.

61. ROBERTS, J. A. F., NORMAN, R. M. & GRIFFITHS, R. 1935. *Ann. Eugen.*, Cambr., 6: 319 and 8: 319.
62. PICKFORD, R. W. 1949. *J. Psychol.*, 28: 129.
63. WILDENSKOV, H. O. 1934. *Investigation Into the Causes of Mental Deficiency.* London: Oxford Univ. Press.
64. PENROSE, L. S. 1938. *A Clinical and Genetic Study of 1280 Cases of Mental Defect.* Med. Res. Council.
65. HALPERIN, S. L. 1945. *Am. J. Ment. Defic.*, 51: 153.
66. (a) NEWMAN, H. H., FREEMAN, F. N. & HOLZINGER, K. J. 1937. *Twins: A study of heredity and environment*, Chicago: Univ. of Chicago Press.
(b) VERSCHUER, O. 1939. *Proc. Royal Soc.*, 128: 62.
(c) GEDDA, L. 1951. *Studio dei Gemelli.* Rome: Orizzonte Medico Ed.
(d) See reference 53.

Symposium: Light from Animal Experimentation on Human Heredity[1]

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Introduction

HUMAN beings are poor experimental material for the study of genetics. This is especially true in studies involving disease resistance or susceptibility where it becomes necessary to infect individuals with bacteria or viruses.

In our studies in human genetics some of our most discouraging problems arise because of inadequate medical records, unreliable information on death certificates, and uncertain pathological diagnoses. If we obtain much of the information which we sincerely desire about ourselves we must get it by indirect methods. Since the same basic laws of inheritance apply to man and other forms of animal and plant life and since many parallelisms in heritable characteristics occur in man and other organisms much help can be had by the more intensive study which is possible with these organisms.

Much of the information which we desire can be secured only when pure lines can be used. Since this is impossible in human beings indirect evidence from other organisms must be used.

What elements are important in disease resistance? Are genes involved, or is resistance due to natural or passive immunity? Does resistance apply to all diseases, or is it specific for each? Does the genotype of the host determine resistance, or must the genotype of the pathogen also be taken into consideration? Does the occurrence of cancer have a genetic basis? Is it specific for each type, or is it general? What is the pattern of inheritance? Is there a genetic basis for resistance to tuberculosis? What is the mechanism involved and how is resistance inherited?

In the domestication and selection of the Norway rat can we find changes which might be paralleled in the civilization of Man? These and many other vital questions will be dealt with in the papers to be presented.

When we ask such questions about human beings and then attempt to answer them by experimenting with mice or other organisms we always take a certain amount of chance that the generalizations will not apply. It is essential therefore that we have as complete a picture as possible of the conditions found in man before such generalizations are made. In order for us to secure even a fair understanding of the many complicated problems dealing with human

[1] Symposium presented at fifth annual meeting of The American Society of Human Genetics at Ithaca, New York, September 9, 1952.

inheritance we must utilize every avenue of approach at our command both direct and indirect. Information secured from animal experimentation can certainly serve as a light by which we can better see our way in our investigations in human genetics.

1. Domestication of the Norway Rat and its Implication for the Study of Genetics in Man[1,2,3]

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PRIMITIVE man did not know about social security, old age pensions, unemployment insurance, and the many other devices that protect us, as members of an organized society, from stress of all kinds.

I bring this up because I want to consider with you today the genetics of structural and functional changes that may have occurred, specifically in the adrenal glands and sex glands during the course of man's adaptation from his primitive unprotected environment to the highly protected environment of our modern civilization. I want to postulate that changes in the adrenal cortex may account for the increasing incidence of such hypersensitivity diseases as rheumatoid arthritis, asthma, and perhaps some forms of mental illness, and that changes in the gonadal secretions may account in part for the present day high incidence of certain neoplastic diseases.

Primitive man lived in an environment in which physical strength, endurance and aggressiveness were at a premium. He had to fight for his food, shelter and mates and to protect himself against attack from enemies of all kinds, human and animal, as well as from the elements. In order to survive he had to remain constantly on the alert, ready either to defend himself or to flee. In this environment the strongest, most aggressive individuals survived—the weak and defective were quickly eliminated.

With the growth of community life, the environment changed in the direction of protection, cooperation, and less constant stress. The qualities needed in the primitive state were no longer at a premium. Less fierce, less aggressive individuals could survive. The capacity to "adjust" to others became increasingly valuable.

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[1] Paper presented as part of Symposium on "Light from Animal Experimentation on Human Heredity," at annual meeting of The American Society of Human Genetics, Ithaca, New York, September 9, 1952.

[2] Delivered in a slightly different form as the Menas S. Gregory Lecture in Psychiatry, New York University and Bellevue Hospital, May 3, 1952.

[3] Research currently carried on under a grant from the Office of Naval Research and under a contract with the Surgeon General's Office.

An attempt to determine the physiological changes in man that paralleled this social development faces many difficulties. It is not possible even to make anatomical comparisons between primitive and modern man except between the so-called "hard" parts—the skeleton and teeth.

A more hopeful source of study, therefore, would seem to be animals that likewise have undergone the change from the stresses of the wild state to the security of a protected and controlled environment: in short, animals that have become domesticated.

Not all domesticated animals can be used for this purpose. In most instances the ancestral forms either are not specifically known or have been long extinct, leaving only paleontological and pictorial records of the teeth, skeleton and hair coat.

Of all animals, the Norway rat, the first animal domesticated for scientific purposes,[4] is an outstanding subject in which to follow the structural and functional changes that occur during the process of domestication, changes that may indicate how the progress of civilization has affected man. It has the following advantages:

First, live wild Norway rats are readily available in large numbers literally at our door-steps, and equally large numbers of domesticated rats are available in laboratories throughout the world. Thus, comparisons of every type—anatomical, physiological and behavioral—can be made.

Second, since the domesticated Norway has been used in almost every field of biological research, we probably know more about it than any other animal except man. It is of special interest that much of our knowledge of adrenal and gonad histology and physiology comes from work on this animal, and that it has also been the favorite animal for studies on stress.

Third, though wild and domesticated Norway rats will breed with one another, neither breeds with any other rat, not even with the Alexandrine, the next most common rat in the world.

Fourth, the comparatively early age at which the rat matures makes it possible to follow the inheritance of various characteristics throughout many generations within a few years' time.

Finally, the Norway rat is similar to man in various ways, particularly in dietary needs, geographic distribution, world population, and colony formation.[5]

[4] When, where and under what circumstances, the Norway first made its appearance in a scientific laboratory is not known. We do know that as early as 1856 a French physician, Philipeaux, used rats for his experiments on the adrenal glands.

[5] The only other animal that even begins to offer the same opportunity for this type of study is the rabbit *Oryctalagus cuniculus* which has been widely used for food and fur and whose ancestors are still living in the wild state in Europe. Nachtsheim has given an excellent account of this animal's domestication in his book "Vom Wildtier zum Haustier." In many ways the Norway rat and the rabbit have undergone the same changes during the process of becoming domesticated. Eickhoff (1949) has used this rabbit for his important studies on the part played by the thyroid in reactions to stress.

In my laboratory we have used over ten-thousand wild rats during the past 10 years for studies in the fields of nutrition, endocrinology, toxicology and rodent control. Simple, effective methods have been devised for trapping, housing and handling these rats. (Emlen, 1944; Richter and Emlen, 1946)

The most important of these devices is a holder, designed by Dr. John Emlen, (1944) by means of which we are able to remove wild rats from their cages, weigh, inject, tube-feed them; and return them to their cages—all without the use of an anesthetic or any danger of being bitten and at the same rate that these procedures can be carried out on domesticated rats. We also use this device in holding and etherizing wild rats for operative procedures.

The wild Norway rat, like primitive man, lives in an environment in which it must constantly be on the alert and often has to fight for its very existence. It has to defend itself against all kinds of enemies, other rats, dogs, cats, owls, and snakes, as well as against man. It is a fierce, aggressive, suspicious animal that attacks at the least provocation and in captivity takes advantage of every opportunity to escape, remains suspicious and tense, and breeds poorly.

In marked contrast, the healthy domesticated Norway is tame, gentle, trusting; does not bite unless frightened or hurt, and makes no attempt to escape. It lives placidly in the controlled environment of the laboratory where food, water, shelter and safety are constantly assured. Its only contributions to its own survival are that it feeds, waters, and grooms itself, and that unlike the captive wild rat, it mates freely, reproducing at an early age and at a rapid rate. Like other domesticated animals it has shown numerous mutations. Castle (1947) has recently listed 23 strains that breed true.

We have sought to determine precisely the ways in which the domesticated Norway in the laboratory differs from its wild ancestor. Comparisons have been made between domesticated rats from our colony, which has been in existence for over thirty years, and wild rats. Our original albino stock came from the Wistar colony; a few piebald and hooded rats from the colony of Dr. E. V. McCollum were introduced about 27 years ago. Since then no new strains have been introduced. In physiological responses as well as in the weights of the various organs and glands, our rats are very like those of other laboratory colonies, so it is likely that they are representative of domesticated rats in general.

Our domesticated rats have been maintained under essentially the same environmental conditions throughout. The rats are fed a stock diet[6] which maintains good health and reproduction. The temperature of the room is kept as constant as possible without air-conditioning, averaging 77° and fluctuating between 75° and 85°, except on a few very hot days in the summer when it occasionally reaches 90° or above. The laboratory is artifically lighted during

[6] Graham flour 72.5%, casein 10%, skim milk powder 10%, butter 5%, calcium carbonate 1.5%, and sodium chloride 1.0%.

the daytime and always darkened at night. Care is taken to minimize all disturbing noises or changes. The breeding rats are handled individually about once each week when the cages are cleaned and changed.

No effort has been made to breed the rats for any special characteristics, except over a short interval of 2 to 3 years when female rats that proved to be unusually active in the activity cages (revolving drums) were regularly returned to the breeding colony. At no time during the 2 to 3 year period did they constitute more than 20 per cent of the breeding females. It is possible that some unconscious selection of less fierce, more tractable rats was practiced.

The wild rats were trapped in the city of Baltimore or on outlying farms, and were used either within a few days or after weeks or months in the laboratory; some were bred and their offspring studied, others were shot in the wild state (on farms) and autopsied within minutes.

The experiments and observations that I am about to describe were carried on over a 10 year period in collaboration with Susan Baker, Miguel Covian, Sally Dieke, John Emlen, William Griffiths, Charles Hall, David Mosier, John Neustadt, Katherine Rice, Philip Rogers, Eberhardt Uhlenhuth, Henry Wagner, David Wood, and James Woods.

Now as to our results. We have not yet discovered any differences in the skeleton or teeth, except that the domesticated rats are in general smaller at maturity. Comparison of the organ weights of the two strains does however show very significant differences. Some organs have become smaller during the process of domestication, some larger, others develop earlier in the domesticated animal. A more detailed account of these changes was presented in an earlier report. (Richter, 1949)

It is of particular interest that during the process of domestication the adrenal glands have become much smaller while the gonads and secondary sex organs develop at an earlier age in the domesticated than in the wild rats. It is also of interest that the pituitary is larger in the domesticated rats.

A number of other differences in structure and physiology have been found but I shall limit further discussion to the adrenals and gonads.

The adrenals are of special interest for the present discussion because of the vital part played by their hormonal secretions in the reaction of animals to stress. They secrete hormones that aid animals in meeting stress. It has been shown that the secretion of adrenal steroids in the rat is closely paralleled by the amounts of cholesterol and of ascorbic acid in the adrenal cortex, as well as by the amount of stored lipids, as demonstrated by staining with Sudan IV or osmic acid. Sayers and Sayers (1949) have fully reviewed this evidence. Thus, by measuring the concentration of cholesterol or ascorbic acid or stored lipids under various conditions, we have available a measure of the animal's reaction to a specific stressful situation. Evaulation of changes in the amounts

of lipids as indicated by various dyes gives an equally good indication of reaction to stress.

The adrenals are of interest also because of the important part that they play in metabolic regulation. Thus, the retention-excretion ratio of sodium chloride, and consequently, body water retention, is related to the concentration of circulatory steroids from the glomerulosa layer of the cortex. When domesticated rats are fed diets with a low salt content, this layer shows considerable activity, presumably secreting DCA or a similar compound that helps to conserve salt; on the contrary, when kept on diets high in salt this layer becomes depleted of lipids—and presumably secretes little or no hormones. (Greep and Deane, 1949).

Our studies, in confirmation of observations made by Watson (1907) and by Donaldson (1928) showed that the adrenals of domesticated rats have undergone a marked atrophy. They weigh ½ to ⅕ as much as in the wild rats of the same weight. A decrease in cortical tissue accounts for the entire difference. (Rogers and Richter, 1948) However, not all zones of the cortex have atrophied. Mosier has shown (1952) that the capsule is wider in the domesticated than in the wild rat; the fasciculata and reticularis layers are much narrower. The wild rat lacks a definite transition zone between the glomerulosa and fasciculata layers and there are other marked differences in the cytology of the various layers. Except for the glomerulosa layer these differences need not be discussed further.

The adrenals of domesticated rats have decreased not only in size but in their content of cholesterol and ascorbic acid and of the various lipids that stain with Sudan IV, Sudan black and other similar dyes. Nichols (1950), Wood (1952), and Mosier (1952). Sudan IV stained sections of the adrenals of domesticated rats show only a sparse deposition of lipid in the fasciculata zone and even smaller amounts in the glomerulosa and reticularis zones, as compared with the wild rat.

We have learned, further, that the two strains of rats react very differently to all stress producing situations: confinement in a cold room at 2°C, fighting other rats, injections with DCA, irradiation, and starvation; likewise to injections with ACTH. In these studies the rats were killed by shooting and the adrenals were removed within seconds.

In the first of these series of experiments rats were kept in a cold room at 2°C for three hours. Some were killed immediately after being removed; others at intervals up to 24 hours. The domesticated rat's adrenals lost most of their lipid; the wild rat's none at all.

Fighting brought out much the same difference. For these experiments we used our so-called 'fighting chamber'—a box 12 x 12 x 18 inches, equipped with a glass front and a floor made of iron rods, spaced ¾ inches apart and

alternately wired to the two poles of an induction coil. Two wild rats placed in this chamber will start fighting almost at once after receiving only a mild shock, each one apparently suspecting the other of having inflicted the pain. An occasional shock suffices to keep the rats fighting. Pairs of domesticated rats do not fight. They spend their time in trying to escape. However, a domesticated rat can be forced to fight by placing it in the chamber with a wild rat. It will defend itself against the attacks of the wild rat. In our experiments the rats were fought for 10, 20 or 30 minutes, and killed either at once or at various intervals after being removed from the chamber. In all domesticated rats, even those killed after the short fighting periods, the adrenal lipid became very sparse or disappeared altogether in all zones. In contrast the wild rat's adrenals showed no loss of lipid even after the rats had been fought for 20 to 30 minutes. In some instances the amounts of lipid actually seemed to be increased.

Injection with DCA gave very similar results.

Irradiation with 400r depleted the lipids from the domesticated rat's adrenals in less than half an hour, but had no detectable effect on the lipids of the wild rat. Results of preliminary experiments indicate that domesticated rats are less able to stand irradiation since at their LD_{50}—720r—we have not killed any wild rats. (Dieke, unpublished)

Starving the rats for 24 hours likewise depleted the lipids from the adrenals of domesticated rats but not of wild rats.

It is of interest then that direct stimulation of the adrenals with ACTH even in amounts as large as 50 mg per animal, did not perceptibly reduce the large amount of lipid in the wild rat's adrenals, whereas in the domesticated rat is caused the disappearance of all except minute amounts.

The changes in ascorbic acid content of the adrenals produced by stress were measured by Woods (1952). He found that fighting, and other forms of stress, produced a great decrease in the case of domesticated rats but none at all in the wild rats.

In brief, the adrenals of the domesticated rats become depleted of lipid and ascorbic acid almost at once after even mild forms of stress; in marked contrast, the adrenals of wild rats do not lose any of their rich supply of lipid or ascorbic acid, even after very severe forms of stress. One possible explanation for these results would be that the wild rat's adrenals can produce hormones as fast as they are being depleted, whereas the domesticated rat's adrenals utilize them faster than they can be produced.

Adrenalectomy has a much less damaging effect in the domesticated rats. They survive adrenalectomy on only small amounts of salt in their diet, whereas wild rats do not survive when given salt in any amount or in any form. (Richter, Rogers and Hall, 1950) They do not survive with any consistency even when treated with cortisone or DCA or both. (Covian, 1949)

A further marked difference in adrenal physiology was brought out by experiments on the effects of feeding salt to the two strains. (Richter and Mosier, 1952) For a period of 70–80 days the rats received salt in their food in concentrations ranging from 2 to 35 per cent. Even in the lowest concentrations most of the domesticated rats lost all lipid from the glomerulosa layer of their adrenals; whereas the wild rats did not lose lipid from this layer even on the highest concentrations.

The results of these various experiments on the adrenal glands indicate that the domesticated rat is much more able to compensate for the loss of the adrenal secretions than is the wild rat. In other words, during the process of domestication the adrenal secretions have come to play a comparatively less important part.

We may now consider the changes that have simultaneously been occurring in the function of the sex glands. Domesticated rats mature earlier than do wild rats as indicated by an earlier opening of the vagina and by reproduction at an earlier age. Further, they mate freely at any time of the year, whereas wild rats mate usually only during the spring and fall, and then not nearly so freely as do domesticated rats at these times. Domesticated rats still retain some of this cyclical pattern since in our colony which is kept under fairly constant conditions, the rats are more active and tend to reproduce more readily in the spring and fall, but they do reproduce readily at all times. Domesticated rats are more fertile. In most colonies practically 100 per cent of females become pregnant when placed for 4 to 6 days with an active male. Many wild rats living in the cities apparently never become pregnant, since Davis and Emlen (1948) failed to find placental scars in a large number of captured wild females, many of them old enough to have had at least a year's opportunity to become pregnant.

A conclusive answer to the question of what changes have occurred in the function of the sex glands would be given by a quantitative study of sex activity of normal and gonadectomized domesticated and wild rats. The effects of gonadectomy would be of special interest, since from the degree of defect produced it should be possible to measure the relative importance of the roles played by the gonads—just as a comparison of the effect of adrenalectomy threw light on the function and relative importance of the adrenal secretion in the two strains. A direct comparison of sexual activity is not possible because the wild rats are loath to mate under observation.

Another means of comparing the importance of the gonadal secretion in the life of these two strains is open to us. This is the study of the effect produced by gonadectomy on spontaneous running activity as measured in revolving drums. Wang (1923) showed many years ago that in domesticated rats gonadectomy has a very profound secondary effect. These rats become very inactive

—about one-twentieth as active as they were before. They gain weight, even though they eat less.

It has now been found that in marked contrast wild Norway rats remain as active after gonadectomy as before; further, they do not gain weight, nor decrease their food intake as do the gonadectomized domesticated rats. (Richter and Uhlenhuth, 1952 A)

It was further found that gonadectomy likewise has little or no effect on activity, food intake and body weight of two other wild species, the Alexandrine rat and the cotton rat. (Richter and Uhlenhuth, 1952 B) Thus, it may prove that a failure of gonadectomy to produce any profound changes in these characteristics is typical for wild animals.

We were interested in finding an explanation for the great reduction in activity that gonadectomy produces in domesticated rats and its failure to produce any demonstrable change in activity of wild rats. It occurred to us that the wild rat might have an auxiliary source of androgens and estrogens—possibly in the adrenals. The finding that after gonadectomy the secondary sex organs were as small or even smaller in the wild than in the domesticated rats seemed to eliminate this explanation.

It occurred to us next that differences in the amounts or character of the adrenal secretions might account for the difference in the effect of gonadectomy. In other words, that the secretions from the larger and more active adrenals of the wild rats might help to keep them normally active after the gonadal secretions had been removed. To test this theory, treatment with cortisone, DCA or Compound S was started in domesticated rats immediately after gonadectomy. It was found that all three compounds prevented the sharp fall in activity, increase in body weight, decrease in food intake, and that cortisone and Compound S maintained the running activity at its preoperative levels.

Thus, the conclusion would seem justified that during the process of domestication adrenal hormones have become less important and gonadal secretions more important in the life of the Norway rat.

Experiments in progress at the present time indicate that wild and domesticated rats respond very differently to hypophysectomy—particularly so far as running activity is concerned. In earlier experiments it was found that hypophysectomy reduced the running activity of domesticated rats to a very low level, even lower than that found after gonadectomy. The wild rats appear to remain quite active after hypophysectomy, not as active as normally or after gonadectomy, but still far more active than the domesticated rats.

At this point I should like to recall to your attention the finding that the pituitary is larger in the domesticated than in the wild rat. This may mean that in the domesticated rat this gland has hypertrophied as a result of its effort to maintain the failing target organs, especially the adrenals. It may also mean that in the wild rats the target organs have a greater autonomy and need less

stimulation from the pituitary. In contradiction of the latter explanation is the fact that hypophysectomy produces very different effects on the adrenals in the two forms, as revealed by both histological and histochemical studies.

These many observations indicate that definite differences exist between the present day domesticated rat and its wild ancestor. Unfortunately, our knowledge of the course of these changes from the wild ancestor to the present day domesticated rat is still very limited. That such changes probably progressed gradually is likely from observations made by ourselves and others who have had colonies for any length of time. Over the course of years the rats become tamer, less fierce, and less apt to bite, or to attempt escape. The most valuable information on the probable progress of events in this interval comes from observations made by King and Donaldson, (1929), and King (1939) pioneer workers on domestication of the wild rat, in which they attempted to reproduce the entire domestication process under controlled conditions. They started with 6 wild rats and bred them through 25 generations. They found that in general from one generation to the next gradual changes in organ weights and behavior occurred, all of which were in the direction of the present day domesticated animal, but by the 25th generation had not yet reached the average levels of the domesticated rats.

We may now inquire into the possible stimuli which induced these changes and consider the environmental and genetic factors concerned. Environmental factors would include the effects of eating the stock diet over long periods of time; living in a room with a fairly constant temperature; being handled at regular intervals by laboratory helpers. For instance, the daily ingestion of large amounts of salt from weaning might have a consistently depressant (but not genetic) effect on the adrenals of each generation. If this dietary factor were the only cause involved, the effect should also gradually disappear when the rats are put on another diet.

Other environmental factors to be considered are those acting on the rats during their lifetime to produce behavioral differences, such as differences in the life experiences of the wild rat and the domesticated rat. To analyze these differences it will be necessary to obtain baby rats from the field or first generation offspring born in the laboratory to captured pregnant wild rats and raise them with a control group of domesticated rats, all the while maintaining identical conditions of diet, temperature and handling. Some studies have already been made on such first generation captive wild rats. We know that they grow up to be less suspicious, less fierce, and more tractable than their parents, though they are still very excitable, bite readily, and will make use of any opportunity to escape.

Similarly, it would be profitable to study the effects produced on organ weights and behavior by placing domesticated rats in the environment of the wild rat in city blocks and farms. Recapturing them at a later date and studying

any changes produced should add to our knowledge of the effects of lifetime environmental influence.

Both of these suggested experiments to control the environment could also serve to isolate the genetic factors of the two strains of Norway rat. Cross-breeding experiments may also be used for this purpose. It has been found that the weights of the adrenals and preputials of the hybrids tend toward those of domesticated rats. The most conclusive evidence will come from experiments in which fertilized eggs from wild rats are implanted into domesticated females and vice versa.

Of special interest from the point of view of genetics is that the number of fungiform papillae on the tongues of domesticated rats is definitely smaller—for domesticated rats 178.3 as compared to 212.9 for wild rats. (Richter and Fish, 1946) We have here an opportunity to put a genetic study on a numerical basis.

Selection seems to have played the most important part in the production of the differences between these two strains. By selection we mean here not the natural selection of wild rats in their natural habitat where the wildest, fiercest, and strongest—the fittest for the environment—survive, but selection in the artificial environment of the laboratory, where the fittest for this type of environment survive—those that are most tame, gentle and fertile. The two life stages in which this selection process has the most effect are during mating and nursing. In captivity wild rats do not mate well. In only a few out of many instances when rats are put together does a pregnancy result. In each instance it is likely that it is the tamest rats of any group that mate. This will be true of mating in each successive generation, so that the tamer rats will be more apt to propagate their own characteristics, including their presumably smaller adrenals. After the young are born, wild mothers frequently eat the entire litter, especially if they are disturbed, so that at this stage an even more severe screening for tameness occurs. The rats that do survive these two stages must be the least apprehensive and through successive generations should produce progressively tamer animals.

Thus we can think of three types of selection: (1) "natural" selection in the unprotected environment of the wild state; (2) controlled selection by man in captured or domesticated animals by breeding; (3) "natural" selection in a protected or artificial environment.

The results of these studies have given us a glimpse into the realm of changes that may occur in a large animal population when the animals are taken out of their free environment and placed in a controlled environment.

It may be asked now whether the knowledge obtained from this glimpse can be of any help in throwing light on what has happened or may still be happening to man during the process of his becoming domesticated or civilized.

We know that man, like the wild Norway rat, originally lived in an environ-

ment in which he had to search for his food, provide his own shelter, fight for his mates—an environment, in short, in which his fitness, hence his survival, was measured by his physical activity, aggressiveness, and ability to withstand violent change. But with the growth of communities and the consequent increase in daily peace and security for the individual, a new environment developed or may still be developing, in which man is largely protected from enemies, and his food, shelter, and livelihood are guaranteed. Man thus may have worked out a controlled environment for himself in which a transformation occurred, somewhat like that undergone by the Norway rat in its adaptation to colony life in the laboratory, resulting in an increase and perhaps even the predominance of the progeny of the so-called weaker, the milder, "better adjusted" individuals.

Here, just as in the domestication of the rat, a selection process—the selection of the "fittest" for this type of environment—must have played the most important part.

This process of domestication has gone quite far in our present day society. Man is now protected almost from the cradle to the grave with all kinds of devices—such as family welfare, social security, unemployment insurance, old age pensions, police protection.

The Romans of the Second Century apparently had achieved an even higher degree of social security and protection. According to Carcopino (1941)—the author of a most interesting book—"Daily Life in Ancient Rome"—80 to 90 per cent of the inhabitants at that time of the great capital city, Rome, depended for their livelihood on public funds—and everyone enjoyed at least one day of holiday for each day of work.

The ultimate in the direction of social security and with it control of man, toward which many people believe we are heading, has been described by Orwell in his book "1984"—a not too happy picture in which security has been developed to such a high degree that man's every movement and even thoughts are observed and directed through a two way television arrangement. Orwell's idea of man's life in 1984 closely resembles that of our domesticated Norway rat—"happily" living out its caged existence.

It is clear that man has undergone great changes in behavior during the long years of domestication. We do not know, however, what anatomical and physiological changes have occurred—especially in his adrenal and sex glands. It has not been possible to make comparisons of adrenal weights, the ascorbic acid and lipid content, or of weights and histology of the gonads, in typical representatives of primitive man and modern man.

There are, however, indirect indications that marked changes may have occurred in these glands. At the present time it has been estimated that over 12 million individuals in this country suffer from hypersensitivity diseases, rheumatoid arthritis, asthma, and some mental diseases—all of which may have their orgin in deficient functions of the adrenal glands since they respond so

remarkably to treatment with cortisone and ACTH. That a permanent deficiency underlies these diseases is known from the fact that treatment with cortisone and ACTH gives relief only so long as it is continued.

Similarly we know that many individuals suffer today from neoplastic diseases—some of which apparently have their origin in or are greatly influenced by a hyperactivity of the gonads since reduction or elimination of the gonadal secretion through castration so remarkably arrests the growth of these neoplasms and treatment with sex hormones greatly accelerates their growth.

It would be of interest to know whether these two groups of diseases likewise were so prevalent at the height of the Egyptian and Roman civilization.

Should it turn out that changes in these glands have actually paralleled man's integration into highly organized societies, we would want to know what can be done about it. How can we correct these undesirable secondary effects? Certainly this would be a problem for the human geneticist as well as for the sociologist and psychiatrist. We might get help, however, from observations on the anatomy, physiology and behavior of domesticated Norway rats that have been returned to the wild environment. Do the adrenals and gonads of such animals regain weight levels of wild rats? And if so in how many generations? Or will it be necessary to revaluate the advantages and disadvantages of the high degree of protection that we all enjoy in our present day society?

Thus, in summary, the Norway rat, the first animal to be domesticated for experimental purposes, has during the course of that domestication, during its transition from the free environment of its wild habitat to the controlled conditions in the laboratory, undergone marked anatomical, physiological, and behavioral changes. The adrenals have come to play a less important part in its life; the gonads a more important part. The observations of these changes may help us to understand some of the changes that have occurred in man during his transition from this original free environment to the highly protected and controlled environment of modern society.

REFERENCES

CARCOPINO, J. 1941. *Daily Life in Ancient Rome.* London, George Routledge and Son, Ltd.

CASTLE, W. E. 1947. The Domestication of the rat. *Proc. Nat. Acad. Sc. U. S.* 33: 109.

COVIAN, M. R. 1949. Rôle of emotional stress in the survival of adrenalectomized rats given replacement therapy. *J. Clin. Endocr.* 9: 678.

DAVIS, E. D. AND EMLEN, J. T. JR. 1948. The placental scar as a measure of fertility in rats. *J. Wildlife Manag.* 12: 162.

DONALDSON, J. C. 1928. Adrenal Gland in Wild Gray and Albino Rat: Cortico-Medullary relations. *Proc. Soc. Exp. Biol.* N. Y. 25: 300.

EICKHOFF, W. 1949. *Schilddrüse und Basedow.* Georg Thieme, Stuttgart, Germany.

EMLEN, J. T. JR. 1944. Device for holding live wild rats. *J. Wildlife Manag.* 8: 264.

FISH, H. S. AND RICHTER, C. P. 1946. Comparative number of fungiform and foliate papillae on tongues of domestic and wild norway rats. *Proc. Soc. Exp. Biol.* N. Y. 63: 352.

GREEP, R. O. AND DEANE, H. W. 1949. The cytology and cytochemistry of the adrenal cortex. *Ann. N. York Acad. Sc.* 50: 596.

KING, H. D. 1939. Life processes in gray norway rats during fourteen years of captivity. *Am. Anat. Mem.* No. 17.

KING, H. D. AND DONALDSON, H. H. 1929. Life processes and size of the body and organs of gray norway rat during ten generations in captivity. *Am. Anat. Mem.* No. 14.

MOSIER, H. D. JR. In press.

NACHTSHEIM, H. 1949. *Vom Wildtier Zum Haustier*. 2nd Ed. Paul Parey, Berlin and Hamburg.

NICHOLS, J. 1950. Effects of captivity on adrenal gland of wild norway rat. *Am. J. Physiol.* 162: 5.

ORWELL, G. 1949. "*1984*" Harcourt, Brace and Co. New York.

PHILIPEAUX, J. M. 1856. Note sur l'extirpation des capsules surrénales chez les rats albinos. (Mus rattus). *C. R. Acad. sc.* 43: 904.

RICHTER, C. P. 1949. Domestication of the norway rat and its implications for the problem of stress. *Proc. Ass. Res. Nerv. Ment. Dis.* 29: 19.

RICHTER, C. P., ROGERS, P. V. AND HALL, C. E. 1950. Failure of salt replacement therapy in adrenalectomized recently captured wild norway rats. *Endocrinology* 46: 233.

RICHTER, C. P. AND MOSIER, H. D. JR. 1952. In press.

RICHTER, C. P. AND EMLEN, J. T. JR. 1945. A modified rabbit box trap for use in catching live wild rats for laboratory and field studies. *Publ. Health Rep.* Wash. 60: 1303.

RICHTER, C. P. AND UHLENHUTH, E. H. 1952A. In press.

RICHTER, C. P. AND UHLENHUTH, E. H. 1952B. In press.

ROGERS, P. V. AND RICHTER, C. P. 1948. Anatomical comparisons between the adrenal glands of wild norway, wild alexandrine and domestic norway rats. *Endocrinology* 42: 46.

SAYERS, G. AND SAYERS, M. A. 1949. The Pituitary-Adrenal System. *Ann. N. York Acad. Sc.* 50: 522.

WATSON, C. 1907. A note on the adrenal gland in the rat. *Jour. Physiol.* 35: 230.

WANG, G. H. 1923. The relation between 'spontaneous' activity and oestrous cycle in the white rat. *Comp. Psychol. Monogr.* 2: 1.

WOODS, J. W. In press.

2. Humoral and Cellular Elements in Natural and Acquired Resistance to Typhoid[1,2]

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SIXTY years ago investigators, beginning with Flugge, Nuttall, Buchner, and Ehrlich, had developed a humoral theory of resistance whereby the blood

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[2] Journal Paper No. J.-2179 of the Iowa Agricultural Experiment Station, Ames, Iowa. Project No. 1180.

plasma carried immune bodies which precipitated, agglutinated, or otherwise fixed pathogenic elements. Lysins, complements, amboceptors, toxins, and antitoxins were introduced as further concomitants of the humoral elements in the disease reactions. The attitude was one of doubt that phagocytosis of bacteria by leucocytes as observed by Metchnikoff and his group was the determining element in natural resistance. Attempts were made to base a theory of natural immunity on humoral elements known to be products formed in acquired resistance. Research over the intervening years has brought the theories closer together in that as evidence was accumulated it suggested that humoral elements may be the products of the leucocytes. The humoral elements have significance to immunity acquired after contact with the disease. It still remains to be shown if these elements are of importance in the first contact when natural resistance must exercise its effect. Besides the specialized cells and their possible products a cell constituent has become increasingly important in interpreting all life processes. The genes which are carried in the chromosomes of each cell are assuming greater significance to disease resistance. Questions of how these genes act on the organism as a whole and in the disease syndrome are of basic importance to the earlier theories of humoral and cellular elements in resistance. In a few cases a single gene difference is sufficient to make the difference between susceptibility or resistance to a disease. In other cases more genes are involved resulting in a more complex inheritance and resistance graded in its expression. The graded series may arise through differences in either the genotypes of the hosts or the genotypes of the pathogens initiating the disease syndrome.

The level of mortality and morbidity to a constant dose of infectious typhoid in domestic fowl or mice for example, is dependent upon the proper relations between the genetic constitutions of the pathogen and of the host. In a sense, disease severity is built on a square, figure 1. On one side of this square are the genetic constitutions of the hosts. At one end specified doses of the pathogen cause complete mortality to hosts of the highly susceptible constitution. In the middle like doses induce 50 per cent deaths. At the other end, similar doses scarcely affect the activities of the hosts, let alone cause death.

The genetically different typhoid pathogens are on the other side of the square. At one end a genetic line of the organisms is practically innocuous to any strain of the host. In the middle the genetics of the line endow it with capacities to kill most of the susceptible mice, allow the survival of about 50 per cent of the medium susceptible mice, and nearly all of the resistant mice. At the other end the virulence of the pathogen line is so great that some mice of even the resistant strain die when inoculated with the standard dose of organisms.

Over the surface of the square the different genetic constitutions of host and pathogen fit together in such a manner as to give all types of disease

reactions. This key to lock type of mechanism of disease mortality suggests the next steps to be taken if disease is to be understood. Information is needed on what the genes do to the hosts in making them susceptible or resistant.

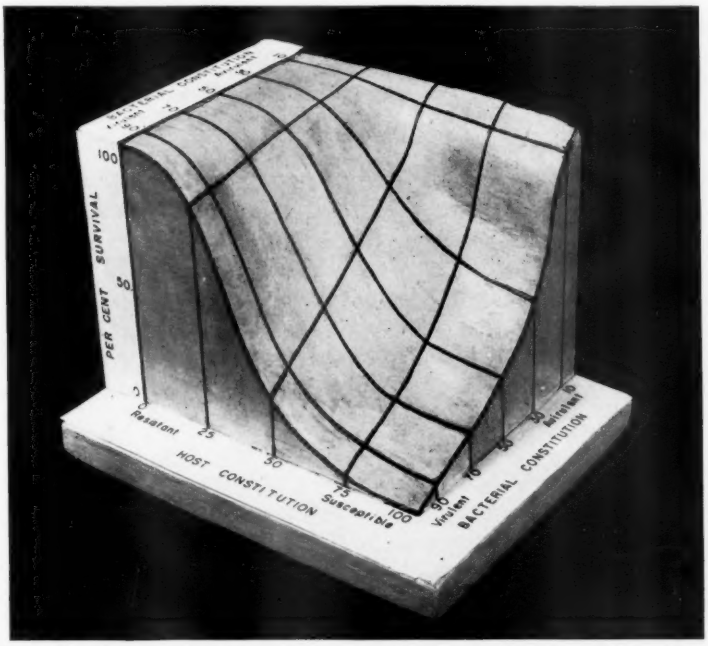


FIG. 1. Model showing interrelation of genotypes of host and pathogen in controlling the severity of a disease. Genotypes of the hosts, ranging from resistant to susceptible, are shown on the front side of the square. The genotypes of the bacteria or other pathogens are shown on the Y axis. The severity of the observed disease produced is shown by the heights above the plane measured in terms of per cent survival of the hosts after the disease has run its course.

Variation in Host Genotypes as a Cause of Variation in Disease Severity

The genetic constitutions of the host cause many different types of disease without any other cause being present. In development from the egg to the infant, in the adolescent, and finally in the senescent adult particular genes may cause morbidity and death to what has up to that time been a well functioning individual. Rh blood factors working in pregnancy, factors for diabetes mellitus operating at any period after birth, the gene for Huntington's chorea coming into expression only after the prime of life has passed are but examples of thousands of genes which have now been studied and shown to be agents of disease in their own right (Gowen 1948).

These genes are capable of extending their effects through a population just as so called infectious diseases spread. At the moment recessive genes

causing dwarf calves and ultimate early death in Hereford, Shorthorn and Angus cattle have become so widespread as to cause real concern. This spread has been facilitated by the heterozygote having a form particularly desired by breeders of feeder and exhibition cattle. Other genes showing like pandemic possibilities as atresia coli in horses and hairlessness in cattle are well known. In man conditions of achondroplastic dwarfs and brachydactyly of the fingers familiar to us today were respectively recorded by the Egyptians around 3500 B.C. and by the Romans during their rise to power. Genes of this type may ultimately be more important for the race than so called infectious pathogens. They are truly cellular elements in which the normal alleles lead to an unrestricted life for the organism and the reciprocal alleles result in morbid conditions of more or less severity.

The purpose of this paper is not, however, to discuss these genes; it is rather to confine ourselves to the interrelations between the genotypes of host and external agents in infection and disease severity. Research on plants and their diseases is on the whole more advanced than that on the animal disease. Two animal investigations should be mentioned as setting a pattern to subsequent studies. In the liver disease of mice caused by the long rod bacillus *B. piliformis*, Tyzzer (1917) observed a case where susceptibility to this disease shows a species difference that is open to analysis since the host species will cross. As the number of mice involved is not stated the case is incomplete but for the *Mus musculus* strain the brown agouti had only two deaths whereas for the *Mus bacterianus* the waltzing strain had 144 deaths. The F_1 to F_4 together with the backcrosses indicated an inheritance of the resistance. Gowen and Schott (1933b) some twenty years later were able to repeat this study, by feeding infected liver material. For *Mus musculus* of 37 mice tested none died; for *Mus bacterianus* of 99 mice tested, 80 died. The F_1 expressed resistance, 14 died in 89 tested. The backcross tests showed segregation according to the parent strain entering the backcross; 4 died to 71 lived, or 5 per cent, when the F_1 was mated to *Mus musculus*; and 38 died to 30 lived, or 56 per cent, when the F_1 was mated to *Mus bacterianus*. For this cross the tentative hypothesis of a single major factor difference between the two strains responsible for the mortality differences expressed by the two species seems reasonable. Other strains of the *Mus bacterianus* may have more complex genotypic differences however. Such differences were shown by a strain derived directly from a stock imported from Peking. The mode of action of the gene complex is not known in either case.

The second case is particularly applicable to this discussion since the inheritance directly affects the humoral element, complement. Rich (1923) in studying Guinea pigs found pigs from which he established a strain free of complement, as distinct from those of normal high complement titer. Genetic analysis showed that the difference was dependent on a single gene pair, the

no complement condition being recessive. The pigs of each group were later infected, spontaneously and by inoculation, with *Pasteurella suiseptica* and *Salmonella cholerae suis* with similar results in each case. Mortality in the complement-free pigs was 77 per cent, while that for the full complement pigs was 20 per cent. Later work showed that the recessive condition altered a hitherto unknown specific portion of the complement thus preventing it from performing its specific function. Here the gene as a cellular element operates through forming a humoral element having a direct part in the disease reaction. But few diseases show such simplicity. Ordinarily many different pathways are important to the full expression of a disease with the consequence that many genes of both host and pathogen are involved.

Typhoid of the Mice

This is true of the typhoid disease of the mouse due to *Salmonella typhimurium*. Within mice there is much variation of genotypes. This variation makes it possible to separate out strains which are resistant, strains of intermediate resistance, and strains which are susceptible to a given line of the pathogen. This separation of the host reaction to typhoid has been accomplished in several ways. In our laboratory, strains are maintained that have the following characteristic survival values when inoculated with 200,000 organisms of our line 11C of *Salmonella typhimurium*; S 86 per cent, RI 82 per cent, Z 58 per cent, K 54 per cent, E 38 per cent, L 12 per cent, and Ba 1.5 per cent. Each survival percentage is based on more than 1000 animals. The typhoid reaction of each strain is as characteristic of the strain as that of any other inherited attribute. Over a period of 15 years, the breeding animals of each successive generation have had no known contact with the disease yet their progeny have maintained their relative resistances in each successive generation.

The genetic effects extend to morbidity as well as mortality. Mice of the resistant *S* strain at the same place in the disease cycle are not as morbid as those of the *Ba* strain, Figure 2.

What Elements are Important to Disease Resistance

In this first contact with the disease, the natural resistance of the strains is not dependent on any demonstrable agglutinins or bactericidal powers present in the blood. In fact agglutinins, i.e., appear in the blood so late in the disease cycle as to be seemingly ineffective as agents to modify the initial course of the disease. The lack of humoral elements of importance to the disease reaction is brought out in other ways.

Matings of males of the most resistant strains with females of the most susceptible strains and vice versa were shown by Hetzer (1937) to give progeny with similar resistance; resistant male x susceptible female 87 per cent survive

for 141 mice; susceptible male x resistant female 89.2 per cent survive for 173 mice. Crosses of resistant males to susceptible females gave progeny which were resistant. This in itself is proof against the transmission of passive humoral immunity from one generation to the next for, as far as is known, males in mammals do not transmit immunity passively to their offspring.

This problem was studied in a different manner by Gowen and Schott (1933c). Susceptible strain females were mated in the same heat period to resistant males and to susceptible males. The two types of progeny in the mixed litters resulting could be separated by their color inheritance; the

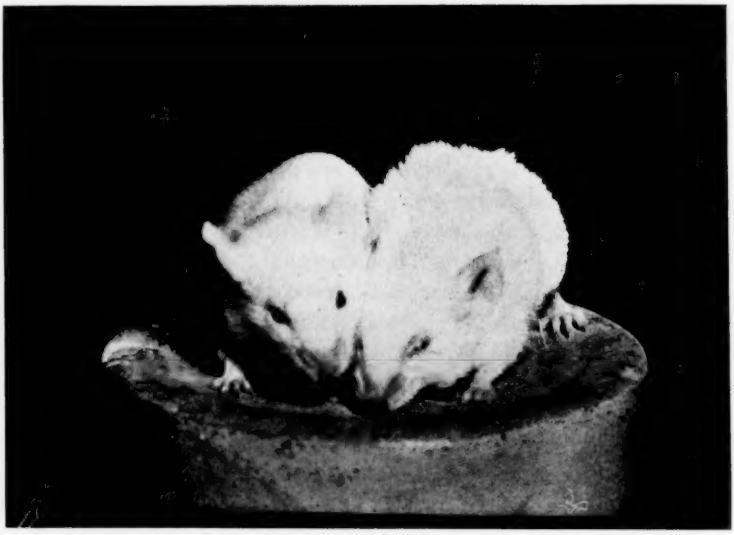


FIG. 2. The mouse on the reader's right is from the susceptible strain. It is very sick. The mouse on the left is from a resistant strain. It shows little effect of the disease. Both mice treated alike.

resistant x susceptible progeny were black, those from the susceptible x susceptible parents were silver in coat color. When tested for their typhoid resistance the two types were not identical in their resistance to typhoid, as would be expected if humoral bodies responsible for resistance were passed through to the fetal blood or through the colostrum to the young. The progeny were different in their resistances but different in the manner called for by their inheritance. The F_1's were resistant as was expected. Progeny with only the susceptible inheritance were susceptible.

The results point to cellular differences in the strains as being responsible for the resistance displayed by the strains when in first contact with the typhoid disease.

Tissue Differences of Importance to Typhoid Resistance

The genotypes of these mice evidently play prominent roles in their natural resistances to typhoid. Tissue elements and their immediate reactions are known to be under gene control. The complexity of these reactions is such that it is unlikely that more than a fraction of the pathways by which the gene controls are exerted are uncovered. Attention was called to the leucocytes by Metchnikoff's observation that bacteria may be phagocytosed by them. In the study of the blood of our six strains of mice Gowen and Calhoun (1943) found that particular numbers of both the erythrocytes and the leucocytes were characteristic of each strain. These characters were inherited to the same degree. The erythrocyte numbers of the different strains were distributed at random with regard to the strains' typhoid resistances indicating that they were not of direct importance to the resistance. The leucocytes on the other hand were directly correlated with the resistance. The leucocytes in the resistant strains were more numerous than they were in the strains showing intermediate resistance. In turn, their numbers in the intermediate resistant strains were greater than those in the susceptible strain. Counts of the different kinds of leucocytes were not important. It was as if the leucocytes came from one common stem cell and that it was the capacity of these cells to divide to form large numbers of leucocytes when necessary that was important.

Other fixed cells of the body as the macrophages of the liver and spleen were shown to play a significant role by Oakberg (1946). Another factor appears of importance for these cells. In susceptible mice, bacteria are readily ingested by the macrophages and large numbers of them may be observed within these cells. These bacteria appear normal, have good staining properties and appear to be reproducing normally. In genetically fully susceptible mice the bacteria seem to increase within the macrophages to the point where they may break out of the cell and become new foci of infection. In resistant mice it was difficult to demonstrate macrophages containing ingested bacteria. This was only possible when the dose given was 100 times that received by the susceptible mice. In these cases the bacteria do not stain well and their cell walls appear ragged. It appears as though the macrophages of the resistant lines have a highly effective digestive enzyme which rapidly destroys the ingested *S. typhimuriums*, whereas the enzyme is in reduced amounts or absent in the macrophages of the genetically susceptible mice.

This was not the only difference in cellular reaction that was important, however. The liver cells of the resistant strains will perform the vital functions of the glycogen cycle and in fat synthesis even in the presence of large lesions, whereas the liver cells of the susceptible mice will not. The organ reactions of the resistant are quite different from those of the susceptible mice. Resistant strains may show extensive lesions of the liver and survive, whereas the sus-

ceptible will die without any clinically evident damage to that organ. By contrast, the naturally resistant mice show but little damage to their spleens although the disease may be severe. Susceptible mice, on the other hand, ordinarily display noticeable lesions in this organ. These observations again call attention to the capacities residing within the cells which are of significance to the disease resistance. The liver cells of resistant mice are able to wall off the large necrotic lesion, block off the spread of the *S. typhimurium*, and neutralize any released endotoxins that may be formed thus allowing the remaining tissue to perform its vital functions.

X-ray Irradiation and Typhoid Resistance

The interpretations presented above are subject to further analysis by means of X-ray irradiation of the animal. These observations emphasize the careful consideration that should be given to any X-ray treatment. Gowen and Zelle (1945) X-rayed 789 mice belonging to our six different strains with dosages ranging from 0 to 700 roentgens incident to the body. All six strai reacted in a comparable manner. Radiation decreased the typhoid resistance of the various strains at the same rate per unit of dosage. The numbers of leucocytes of the different strains were decreased to the same relative amounts by comparable X-ray dosages. It is known that total body irradiation will affect many types of body cells. It cannot, therefore, be concluded that the leucocytes are the only cells which have been affected and that they alone are responsible for the changes in resistance. Rather they are an index to what is taking place in cells of like X-ray susceptibility throughout the body. The X-ray treatments reduced the typhoid resistance of the animal and the numbers of its leucocytes proportionally over the full dosage range. While the leucocytes are not the only cells affected these facts support the conclusion that natural disease resistance is dependent on cellular function and on numbers of the phagocytic cells. These relations furnish independent evidence for the conclusions reached by other methods.

Specificity of Genotypes for Natural Resistance

The question arises, is this condition one where the natural resistance extends to one or all diseases, does the individual have an over all constitution or is the constitution specific for each disease? This question was investigated by Gowen and Schott (1933a) for diseases due to *Salmonella typhimurium*, pseudo rabies and the antigenic poison ricin. The genes required for resistance or susceptibility to one disease were independent of those required for resistance to another. Webster (1933) confirmed this observation for the independence of resistance to louping ill and to typhoid. For bacterial species which are related taxonomically the natural resistance to one disease carries over to that due to its close relative. Typhoid resistance is closely correlated with Pasteurella

resistance but less correlated with Klebsiella or pneumococcus resistance. Similar conclusions may be derived from the data of Schutze, Gorer, and Finlayson (1936) for *S. typhimurium*, *S. enteriditis*, louping ill, Pasteurella and pneumococcus.

Taken broadly the results concur in showing that a resistant constitution for one disease is only likely to indicate resistance to another disease if the two diseases are fairly closely related. When the diseases are of different types, resistance to one tends to be independent of resistance to the others. In this respect inheritance for disease resistance behaves like any other inheritance dependent on many genes, some genes are independent, some appear to be linked or to have more than one effect, some have physiological interactions but it would appear that all are ultimately separable.

Genotypes of the Pathogen

The other side of the square portraying the base of the disease syndrome may now be examined. The genotypes of a species of bacteria are as diverse as those of their hosts. They may have more significance to the disease which is produced because they reproduce in such large numbers. The small rate at which mutations of existing genes occur and the rapidity with which such mutants may replace the existing population becomes of great importance in altering the character of the disease produced. The differences may result in changes in the growth pattern of the colony, in the color, morphology, or antigenic properties of the organism. They may affect the cultural requirement of the organism making some strains require a nutrient for growth which other strains can synthesize. The pathogenic characteristics may be altered in either the direction of greater or lesser virulence. The effects of these changes on disease expression have been under study in our laboratory for some 20 years for such diseases as tobacco mosaic, corn wilt, typhoids of both mouse and fowl. The results are concordant.

Changes occur and may readily be established in all of the pathogens involved. The new types may appear at any time during the experiment and may cover a wide range. With selection it is possible to establish many of the new forms as true breeding types. In a given environment competition may exist resulting in rapid replacement of the unfavored types. Changes in virulence as dependent upon the inherited bacterial constitution have been examined by searching out phenotypical variants in originally pure stocks, Zelle (1942), Lincoln and Gowen (1942), Gowen (1948), Plough, Young, and Grimm (1950), and Gowen, Stadler, Plough, and Miller (in Press). The mutant phenotypes are represented by changes in color or morphology of the colonies, antigenic types of the organism, ability to synthesize amino acids or other metabolites from an energy source and simple salts.

The pathogen's ability to initiate a disease in a host is rather highly specific.

As attained in nature this property represents some chance combination of genes which appeared, was preserved, and improved upon by selection during successive generations of reproduction for better and better gene combinations and the inclusion of any of the more favorable mutations which might have occurred as time passed. Contact with an epidemic indicates that an efficient gene combination in the pathogen has evolved. Changes of a random sort comparable to those resulting from chance mutation would be unlikely to improve the disease producing ability of a highly virulent organism. Our results agree with this interpretation. Mutations of our highly virulent lines on the average lead to lines of less virulence. A study of 12 different mutants of 533-11C requiring adenine as a metabolite illustrate this fact. Seven mutants were avirulent causing no deaths, 3 showed some virulence, 2 were as virulent as the parent. The average virulence after mutation was less than the highly virulent parent type. The mutants were separated because of their effects on adenine. The range in virulence shows that this requirement is not itself the primary cause of virulence. Rather it is some change which through chance was associated with the change to adenine requiring that is of importance.

For avirulent cultures any observed changes in virulence will of necessity be toward greater mortality. Mutations of such lowly virulent forms consequently tend to be accompanied by increases in the mortality of the host. The average result of several mutations would be expected to be an increase in virulence. Eleven mutants occurring in our avirulent line 519 illustrate that fact. One of these mutants, that toward leucine requiring, showed a moderate increase in virulence. The rest remained avirulent. The mutations as they are observed are directional in that they tend to be less virulent when their parent is virulent and more virulent when the parent is avirulent. The particular change in observed virulence is not necessarily related directly to the change by which the mutant was detected.

Mutations toward or away from virulence may occur naturally or through the help of radiant energy from X-rays. Quantitative estimates of the frequencies of these changes and of the types of change have been made for several forms. The mutations can likewise affect the capacity of the pathogen to stimulate active immunity in the host.

Acquired Immunity as a Property of Host and Pathogen

Three factors important to increasing resistance to a disease through vaccination are common knowledge. The fourth factor and possibly the most important is not so generally recognized. In order of the emphasis given them, these factors are (1) the dose of the vaccine administered at any one time; (2) the necessity for vaccinations at successive intervals; (3) the line of the bacteria making the vaccine; and (4) the genotype of the host receiving the vaccine.

The first factor takes cognizance of the fact that if the vaccine is too small in amount, it will not stimulate the recipient to form the antibodies of resistance. If on the other hand the dose is too large the endotoxins, etc., released, will be enough to create lesions and sometimes death. The desirable dosage is that quantity which will stimulate a strong immunity without undesirable affects.

The second point is dependent on the fact that as immunization proceeds a greater and greater dose for stimulation can in general be given.

The strain of pathogen is ordinarily considered by the makers of the vaccine. They recognize that some strains of a pathogen are good immunizers and others are not. This is another way of saying that the inheritance of the particular strain of pathogen, its genotype, is of importance to its immunizing properties.

The genotypes of the hosts which are to be immunized up to recently have been neglected.

An experiment, including more than 4,212 mice, was performed to obtain quantitative information on these questions.

Figure 3a shows the relation between immunization dose and the resistance to a dose of 50 million organisms of our highly virulent culture 11C. The chart shows that for this rather large challenge dose less than 50 per cent of the mice are protected. Protection is greater for those mice receiving the most vaccine. In making these immunizations, however, certain mice die presumably due to release of endoxtoxin in the absorbed vaccine. The mice which succumb are those which are least resistant to a first attack of the disease. The genotype of the mouse is correlated with its ability to actively or passively immunize.

Figure 3b shows that three successive immunizations are better than two, and two are better than one. The improvement in resistance with each step is about the same in amount.

Figure 3c presents clear evidence for the significance of the bacterial genotype in immunization. The typhimurium line which displays little virulence was the poorest immunizer. The other two lines having higher virulence were also better immunizers. The avirulent line and one of the virulent lines came from the third line by one step and by two step mutations respectively. As these bacterial lines come from each other by mutation, the importance of even a gene difference in the lines' genotypes is evident.

Figure 3d shows the effects of the hosts' genotypes on their abilities to immunize. The six different strains immunize differently. The naturally resistant strains on first contact with the disease are those which have their resistances enhanced most by immunization. The intermediate strains, as measured by natural resistance, are likewise intermediate in their abilities to immunize. The most susceptible strains after immunization remain more susceptible than the other genotypes immunized in like manner. The level of resistance of each strain is simply raised a proportionate amount. In terms of

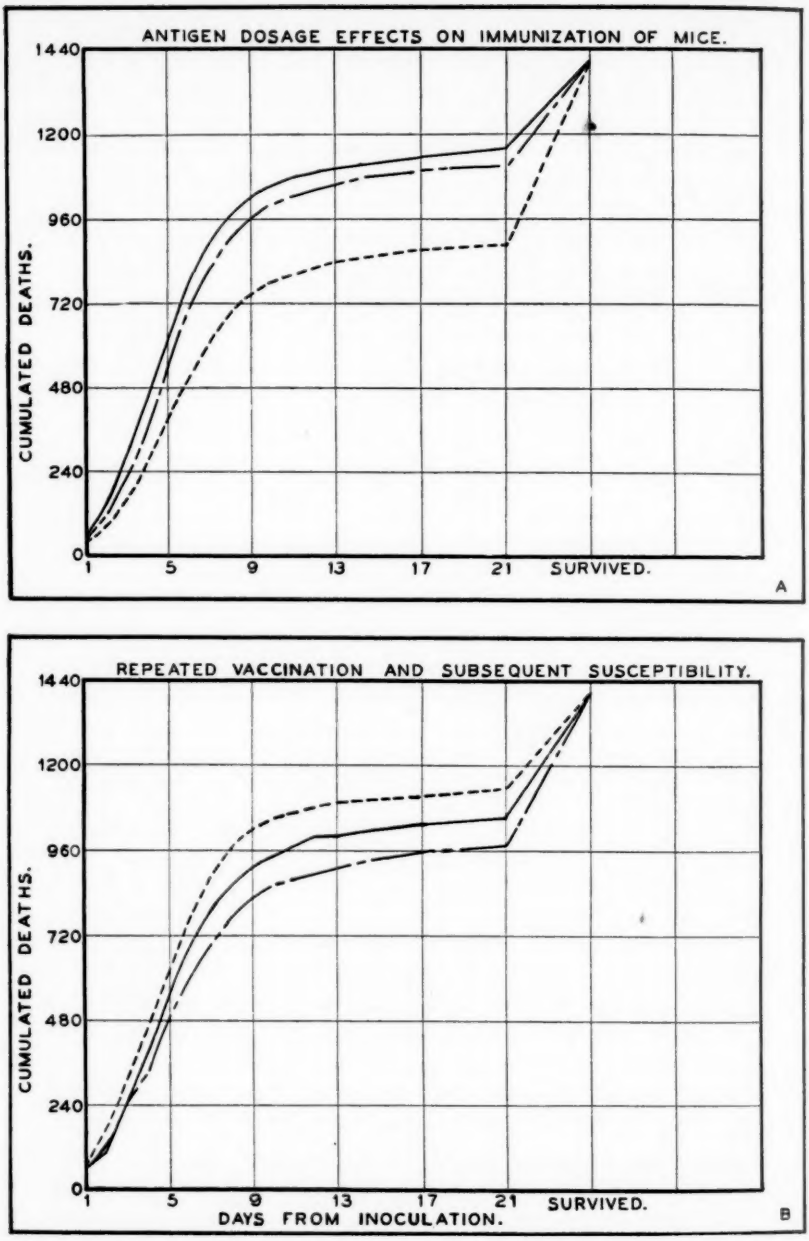
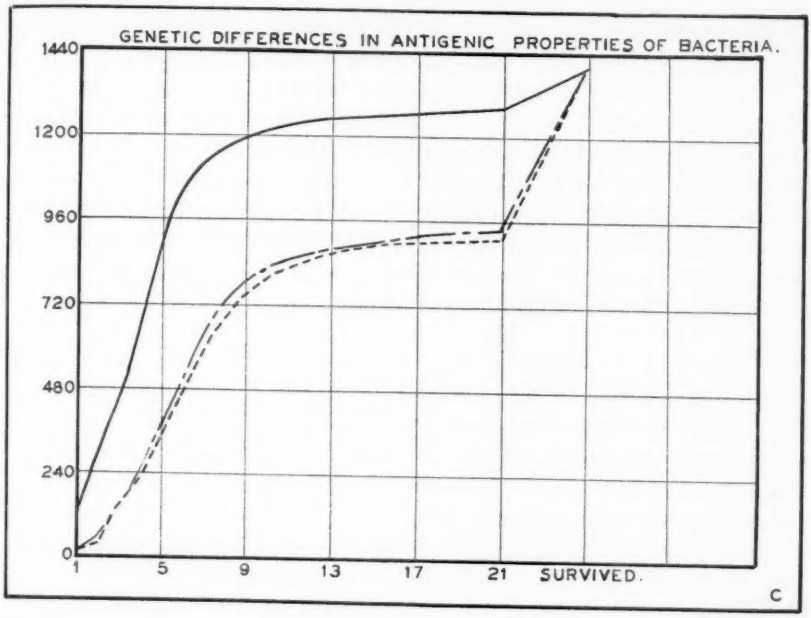


FIG. 3. Resistance acquired through vaccination with heat killed cultures of *Salmonella typhimurium* 11C as related to (a) amount of vaccine administered; (b) times vaccinated; (c) genotypes of bacteria furnishing the vaccine; (d) host's genotype for natural resistance. Graphs show cumulated deaths from inoculation by days during course of disease.


GENETIC DIFFERENCES IN ANTIGENIC PROPERTIES OF BACTERIA.
1440
1200
960
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SURVIVED.
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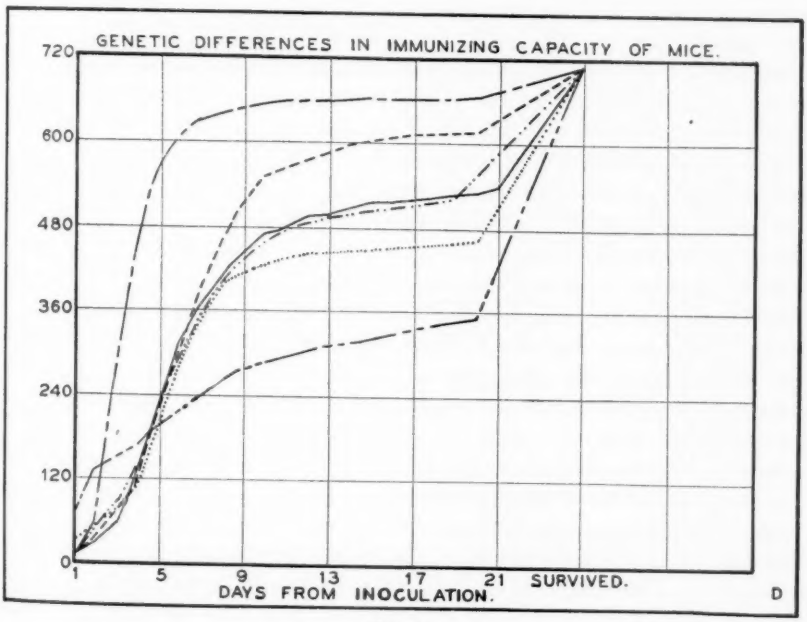
GENETIC DIFFERENCES IN IMMUNIZING CAPACITY OF MICE.
720
600
480
360
240
120
0
1
5
9
13
17
21
SURVIVED.
DAYS FROM INOCULATION.
D

FIG. 3

bacteria which may be inoculated, immunized mice can resist 100 to 200 times as many live virulent strain bacteria as the unvaccinated mice.

In our mice cellular elements show a high correlation with natural resistance. Humoral elements are not found prior to the first contact with the disease. They are not part of the phenotypes of the different strains but are only called out by contact with the pathogens. The effects of the vaccinations parallel those found for natural resistance in that they depend on the genotypes of the hosts and pathogens. These facts suggest that the results attained in acquired immunity to typhoid are due to attributes of the cellular mechanisms which are likewise responsible for natural resistance.

APPLICATIONS TO DISEASE CONTROL

By successive steps medical science has advanced from a concept of disease as due to a single demon as Apollo's arrows, having as its purpose the punishment of man, through the Hippocratic differentiation of disease into different and distinct complexes based upon their clinical symptoms, to the concept that diseases are truly separable and open to proper treatment when the initiating and perpetuating agent or agents are known. Genetical research is carrying forward the traditional objectives of this unfolding thought. Through efforts of workers in the field it is now recognized that agents of diseases and their hosts each are organized and get their characteristics from the development of an inheritance, made up of distinct genes. By specifying the gene for a particular disease reaction it has been possible to show that genes act as protectors from a given disease, as independent of the disease reaction, and as causative agents in the disease syndrome. A clinically manifest disease only results when the proper combination of the genotype of the victim, the genotype of the pathogen, where one is necessary, are properly synchronized with the environment.

This synchronization is illustrated earlier by the full and no complement genes in guinea pigs. The full complement gene governs the formation of normal complement, a humoral substance having several important disease protecting properties. The no complement allele forms a substance like complement in all but one component. That component is essential for resistance to two of the guinea pig's pathogens as well as to the binding of antibody and antigen. These genes operate through a change in a humoral body which they have a part in forming.

The localization of the genes has shown, as with diseases in which pathogens are responsible, that clinically identical symptoms may be due to different causes operating through distinctly different channels. This fact issues its own warning for as Haldane (1948) says "just as the methods for the cure of bacillary and amoebic dysentery are very different, so it is unlikely that the same therapeutic measures will succeed against diseases, however similar in their symptoms, which are due to different genes." Considerations of this kind

emphasize the need for careful study of all cases where inheritance plays a major role in the initiation of the disease.

In considering the probable severity of a disease attack something is often known on the incidence and the severity with which that disease has appeared previously in the family. This information may have considerable value in prognosis. The disease may be detected at an earlier stage than otherwise, making treatment more effective. Information on the inheritance patterns in our mice not only give information on the mortality but it also indicates the severity of the reactions at each successive stage in the disease cycle. Physical characters like weight, muscular activity normally considered in estimation of physical constitution, have little bearing on the outcome. Normal body temperature levels of the mouse do not appear to influence the course of the disease, although in fowl typhoid a fraction of a degree difference in normal temperature appears important. The characteristics of the normal blood have prognostic value. In normal mouse and chicken blood, humoral elements related to their typhoid resistance have been found lacking. The leucocyte number for our mice is related to the observed resistance but is not the whole story, for the phagocytic cells of different strains differ in their ability to destroy the typhoid organism.

The results have a direct bearing on the explosive appearance of a disease in a population (Gowen 1951). The factor making toward this sudden appearance appears to be mutation toward greater virulence of the pathogen. This has been demonstrated several times in *Salmonella typhimurium*, *Salmonella gallinarum*, and in *Phytomonas stewartii*, where saprophytic lines have suddenly changed to virulent forms. The reverse change of virulent to saprophytic types is also demonstrated. Such changes would form a means of preserving the organisms over unfavorable times. The influence of these factors has had unwitting demonstration under field conditions in our major food crops. The factors involved are a host of uniform genotype, contact between individuals sufficiently close to make for easy spread of a particular disease, a pathogen whose genotype fits that of the host in a manner favorable to invasion, high morbidity and mortality. These conditions have been satisfied repeatedly particularly in our cereal crops. In fact, during the last fifty years the conditions have been fulfilled by a succession of quite diverse pathogens able to invade in succession the newer synthesized varieties built up to resist older diseases. In succession strains of rusts and smuts, *Helminthosporium victoriae* and a previously little known crown rust (Murphy 1948–49) have assumed the major pathogen role.

Each host shows a cyclic rise of infection and mortality. Each cycle is highly dependent upon how well the genetic constitutions of the particular host and pathogen fit together. The necessary close contact between susceptible individuals is established by the uniform planting of the same host genotype

over large areas of the suitable agricultural lands. Dosage with the virulent disease is high because of the close contact. Because of the close association of individuals, the susceptible host genotypes, the virulent genotypes of the pathogens, and the large amount of inoculum received by each individual, epidemics of major severity follow.

Considered individually each epidemic comes near meeting the simplest postulates yet devised to account for the rise in epidemic mortality, Brownlee (1906–10), Ross (1915), Soper (1929), Frost (1941), and Wilson (1945). In succession, each different population is composed of a single genotype whose individuals will have identical susceptibilities for a pathogen of a particular genotype. In each case a very small number of the pathogens come into or exist in the region. Because of the host genotype on which to work and the dense plantings of this favorable host making for easy spread, the rare pathogen is able to rapidly outgrow all other types and create massive infections of any remaining plants. The resulting mortality decimates the host. By man's efforts the first host is replaced by a host of genotype resistant to the first disease but susceptible to another which is present in the region again in small numbers. The process is repeated. The successive changes of the host genotypes create successive cycles, first favorable to the host's reproduction and survival, then favorable to the particular pathogen and high host mortality.

In animal or human populations where the genotypes are diverse the above conditions are only partially fulfilled and the severity of the epidemic is consequently modified. The unconscious approach to the ideal condition as found in our cereal crops helps to confirm the significance of host and pathogen genotypes in disease expression.

SUMMARY

This paper discusses the part played by the genes, making up the genotypes of both host and pathogen, in disease causation and severity. Gene differences within a host may act as pathogens to their host, in the sense that they may cause recognizable syndromes, and may spread through successive generations of the population. Gene differences between different members of the host population may be responsible for susceptibility to a given pathogen on the one hand and resistance to the same pathogen on the other. Such differences may be due to a single pair of alleles as for Pasteurella of the guinea pig or to many pairs of genes as in typhoid of the mouse. Genes affect different features of the natural resistance pattern. The paths through which the effects are produced are very imperfectly surmised. Specificity is ordinarily observed for the gene effects on resistance particularly if the pathogens initiating the diseases are taxonomically rather far removed from each other. The specificities of the gene effects for a given disease under natural conditions have most

frequently been traced to cellular differences with humoral differences occurring as a secondary consequence of cellular activity.

Genotypic differences are displayed by individuals within a pathogenic species. These differences modify virulence. Like differences in genotype affect the host's property of acquiring immunity on exposure to a disease. The interactions of the host genotypes with those of the pathogen are basic not only to the initial severity of the disease but also to the level of immunity acquired after the survival of the initial attack. In disease, as it occurs naturally, full expression of these interacting factors together with those characteristic of the environment ordinarily lead to a great variety and complexity of disease reactions. Under certain conditions primary individual factors may be simplified, for example, in an epidemic of cereals, to the point where the parts of the complex interacting system of the disease processes may be recognized and evaluated in terms of each contributing element. When so observed epidemics appear to be generated, to rise in severity, and to fall, as the result of a dense population of susceptible genotypes having in it a few pathogens of the genotype for high infectivity and ordinarily high pathogenicity and virulence for the host susceptible genotype in an environment which leads to selective rapid reproduction of the virulent pathogenic strain and to massive doses to the host population.

REFERENCES

BROWNLEE, J. 1906. Statistical studies in immunity: The theory of an epidemic. *Proc. R. Soc. Edinburgh* 26: 484–521.

BROWNLEE, J. 1910. The mathematical theory of random migration and epidemic distribution. *Proc. R. Soc. Edinburgh* 31: 262–289.

FROST, W. H. 1941. *Epidemiology.* The Commonwealth Fund—New York. pp. 493–542.

GOWEN, JOHN W. 1948. Inheritance of immunity in animals. *Ann. Rev. of Microbiology* 2: 215–254.

GOWEN, JOHN W. 1951. *Genetics and disease resistance.* Genetics in the 20th Century. Chap. 19: 401–429. MacMillan Company: New York.

GOWEN, JOHN W. AND M. LOIS CALHOUN. 1943. Factors affecting genetic resistance of mice to mouse typhoid. *J. Infect. Dis.* 73: 40–56.

GOWEN, JOHN W. AND R. G. SCHOTT. 1933a. Genetic constitution in mice as differentiated by two diseases, pseudorabies and mouse typhoid. *Am. J. Hyg.* 18: 674.

GOWEN, JOHN W. AND R. G. SCHOTT. 1933b. Genetics predisposition to *Bacillus piliformis* infection among mice. *J. Hyg.* 33: 370–378.

GOWEN, JOHN W. AND R. G. SCHOTT. 1933c. A genetic technique for differentiating between acquired and genetic immunity. *Am. J. Hyg.* 18: 688.

GOWEN, JOHN W., JANICE STADLER, H. H. PLOUGH, AND HELEN Y. MILLER. On the chemical basis for typhoid resistance in mice. In press.

GOWEN, JOHN W. AND M. R. ZELLE. 1945. Irradiation effects on genetic resistance of mice to mouse typhoid. *J. Infect. Dis.* 77: 85–91.

HALDANE, J. B. S. 1948. The formal genetics of man. *Proc. R. Soc. London, B.* 135: 147–170.

HETZER, H. O. 1937. The genetic basis for resistance and susceptibility to *Salmonella aertrychia* in mice. *Genetics* 22: 264–283.

LINCOLN, R. E. AND JOHN W. GOWEN. 1942. Mutation of *Phytomonas stewartii* by X-ray irradiation. *Genetics* 27: 441–462.

MURPHY, H. C. 1948–1949. *Breeding oats of improved adaptation, quality, and yield.* Unpublished Annual Repts., U.S.D.A. Bur. Plant Indus., Div. Cereal Crops and Diseases, and Iowa Agr. Exp. Sta.

OAKBERG, E. F. 1946. Constitution of liver and spleen as a physical basis for genetic resistance to mouse typhoid. *J. Infect. Dis.* 78: 79–98.

PLOUGH, H. H., HELEN N. YOUNG, AND MADELYN R. GRIMM. 1950. Penicillin-screened auxotrophic mutations in *Salmonella typhimurium* and their relation to X-ray dosage. *J. Bact.*, 60: 145–157.

Rich, F. A. 1923. Concerning blood complement. *Vermont Agr. Exp. Sta. Bull.* 230: 1–24.

ROSS, RONALD. 1915–1916. An application of the theory of probabilities to the study of a priori pathometry. *Proc. R. Soc. London*, Ser. A., Part I, 92: 204–230; Part II, 93: 212–240.

SCHUTZE, R., P. A. GORER, AND M. H. FINLAYSON. 1936. The resistance of four mouse lines to bacterial infection. *J. Hyg.* Cambr. 36: 37–49.

SOPER, H. E. 1929. The interpretation of periodicity in disease prevalence. *J. R. Statist. Soc.*, London, 92: 34–61.

TYZZER, E. E. 1917. A fatal disease of the Japanese waltzing mouse caused by a spore-bearing bacillus (*Bacillus piliformis*). *J. Med. Res.* 37: 207.

WEBSTER, L. T. 1933. Inherited and acquired factors in resistance to infection. II. A comparison of mice inherently resistant or susceptible to *Bacillus enteriditis* infection with respect to weight, fertility, and susceptibility to various routes and types of infection. *J. Exp. Med.* 57: 819–845.

WILSON, EDWIN B. 1945. Some points in epidemiological theory. *Am. Scientist* 33(4): 246–252.

ZELLE, M. R. 1942. Genetic constitutions of host and pathogen in mouse typhoid. *J. Infect. Dis.* 71: 131–152.

3. On the Mechanism of Genetic Resistance to Tuberculosis and its Mode of Inheritance[1,2]

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OVER the past 20 years, by bother and sister inbreeding of rabbit stocks for over eight generations and subsequent intrafamilial propagation, various races have been developed. These exhibit different native heritable resistance

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[3] Charles Hartwell Cocke Memorial Fellow of The National Tuberculosis Association.

to tuberculosis, characteristic and constant for each race, irrespective of the mode of infection or the virulence of the tubercle bacillus used. Not all of the original races developed are still extant. Of the strains studied, races A and III were highly resistant to the disease, races F, C, Ca and FC were highly susceptible, while races B, D, H and AD were of intermediate resistance.

MECHANISMS OF GENETIC RESISTANCE

The pattern of the pathogenesis of the disease in these different races is most sharply revealed by natural airborne contagion. This is achieved either by exposing the different races simultaneously to rabbit roommates artificially infected with highly virulent bovine type bacilli (4) or by causing them to inhale the same numbers of these bacilli at a single sitting in an apparatus for quantitative airborne infection previously described (6). In the first instance, the susceptible families develop a single primary pulmonary focus which progresses rapidly, undergoes extensive caseation and fails to become encapsulated. Within a few weeks the draining tracheobronchial lymph nodes show caseation and the disease disseminates by hematogenous and lymphogenous routes. The metastatic foci thus originated progress without any effective opposition and the animal dies rapidly of a generalized tuberculosis, characteristic of the disease of white infants or of adults belonging to aborginal races which had not yet been subjected to natural selection by endemic tuberculosis. In the natively resistant rabbits the disease also originates as a single primary focus. However, the lesion in the lung progresses slowly, becomes encapsulated and eventually undergoes liquefaction, ruptures into the bronchi and, by intracanalicular spread of vast numbers of bacilli, gives rise to slowly progressive ulcerative pulmonary phthisis. The bacilli which escape into the lymph or blood cause few if any progressive lesions in the organs focalized, so that the draining lymph nodes and the other organs are not involved. The rabbits eventually die of a chronic disease which is localized at the portal of entry, the lung, and closely resembles the ulcerative pulmonary tuberculosis of the so called reinfection type in white European adults. The pattern of the disease in susceptible and resistant rabbits exposed to quantitative inhalation of bovine type tubercle bacilli is exactly the same as that seen in these respective races exposed to natural airborne contagion, with the single exception that the number of primary pulmonary foci which originate in the lungs is a function of the number of bovine type bacilli inhaled and the number that reach the terminal alveoli.

If bovine type tubercle bacilli are injected into the skin of susceptible and resistant rabbits (4), it is found that the mononuclear phagocytes of the resistant rabbits rapidly acquire an increase capacity to destroy the bacilli and are soon transformed into mature epithelioid cells harboring but few microorganisms. The small numbers of bacilli that escape the local lesion give rise to

chronic ulcerative pulmonary phthisis which eventually kills the animals in 14 to 15 months. On the other hand, the phagocytes of the susceptible rabbits do not readily acquire this capacity, and tubercle bacilli in great numbers swarm in their immature epithelioid cells 4 to 5 months after inoculation when the animals die of an extensive generalized tuberculosis. Associated with this more rapid development of acquired resistance against the multiplication of the tubercle bacillus in the tissues of the natively resistant animal, there is frequently but not constantly an increased capacity to develop, quickly and intensely, allergic sensitivity and antibodies against the tubercle bacillus and its products.

If human type tubercle bacilli are used in quantitative inhalation experiments on natively susceptible and resistant rabbits, it is found (8) that in the vast majority of the former, that had inhaled several thousand bacilli, there is a variable and often extensive pulmonary disease 5 months after infection. By contrast, in resistant rabbits simultaneously exposed and killed at the same time, only rarely is slight pulmonary tuberculosis observed, while in the great majority of these rabbits no tuberculosis at all is seen. Furthermore, while the lungs of susceptible rabbits at this time contain millions of viable tubercle bacilli, the lungs of the resistant rabbits are usually sterile and only occasionally show small numbers of microorganisms. It is noteworthy that the *initial* growth of tubercle bacilli in the lung is more retarded in the resistant animal. Again, as was found with bovine type tubercle bacilli, allergic sensitivity and antibodies tend to develop more rapidly or more intensely in the natively resistant races.

Parallel observations have been made with intracutaneous inoculations of BCG in susceptible and resistant rabbits (9), so that the response to this injection of the attenuated tubercle bacillus can be used as a means of selecting natively resistant and natively susceptible rabbits for breeding purposes. For the nodule at the site of inoculation of BCG in natively resistant rabbits develops quickly, reaches its peak rapidly and soon heals; whereas in susceptible rabbits this nodule grows more slowly, reaches its height tardily and heals much later. Again, the bacilli are more rapidly destroyed in the resistant animal and the development of allergic sensitivity and antibodies is accelerated in these animals. In fact, the larger initial size of the BCG nodule in the resistant rabbit is clearly attributable to the greater intensity of the allergic sensitivity developed by these rabbits in the first week after the intracutaneous inoculation of the several million viable BCG used. Whether the more rapid rate of development of allergic sensitivity and antibodies is the result of the accelerated native capacity for destruction of the bacilli in the tissues of the resistant animal or of the greater responsiveness of their cells to antigenic stimulation or to both has not yet been determined.

During the course of these studies it was observed that there is an incomplete

parallelism between the spread of intracutaneously injected India ink and resistance to tuberculosis (4). One of the most resistant races restricted the spread of the dye, while one of the most susceptible strains permitted it to spread much more widely. In an endeavor to determine to what extent connective tissue permeability determines resistance to the infection (5), it was found that the administration of estrogen, which reduces connective tissue and vascular permeability, retarded the dissemination of cutaneous tuberculosis and increased the resistance to the disease. On the other hand, the periodic administration of chorionic gonadotropin, which induced successive crops of corpora lutea in the ovaries and increased the connective tissue and vascular permeability, enhanced the disseminations of cutaneous tuberculosis and reduced the resistance to the disease. These sex hormones, while they affect the spread of the disease in the connective tissue in opposite directions, do not essentially influence the major factors concerned with resistance, namely, the rate of growth and destruction of the bacilli and the rate and intensity of development of antibodies and allergic sensitivity.

It was noted during the course of the latter investigation that tuberculosis in rabbits is accompanied by an hypertrophy of the adrenal cortex. Furthermore, just as in the case of connective tissue permeability, there was an incomplete parallelism between native resistance and the function of the adrenal cortex as indicated by its mass in relation to body weight (10). Thus the resistant race III is characterized by the possession of large adrenals whereas the susceptible FC strain possesses small adrenals. However, the C rabbits which are highly susceptible also have large adrenals. It is evident therefore that even if adrenal function is a factor in native resistance, it is only one of several. To ascertain whether the adrenocortical hormones play any role in resistance to the disease, cortisone in pharmacologic doses was administered to 10 rabbits of the susceptible race FC, and 10 of their litter mates served as controls (7). These two groups were then simultaneously exposed to the quantitative inhalation of human type tubercle bacilli. Cortisone treatment was continued in the experimental animals for about 5 weeks, at which time both groups were killed and the number, size and histological character of the primary pulmonary tubercles generated was determined. This method of assaying the effect of the cortical hormone on resistance was used because it was found to be the most accurate, rapid and quantitative measure of native resistance.

If bovine type tubercle bacilli of maximum virulence for the rabbit are quantitatively inhaled, it was shown that, irrespective of the genetic resistance of the animal exposed, the ratio between the number of bacillary units calculated as inhaled and the number of gross pulmonary tubercles developed within 5 weeks after infection is constant, namely 3 (6). It was demonstrated by a number of observers that only one of three inhaled particles of the size of

tubercle bacilli is retained in the alveoli of man or animals (1). It follows, therefore, that each viable unit of this bovine strain that is ingested by the alveolar phagocytes yields a visible pulmonary focus. On the other hand, if rabbits of different genetic resistance inhale human type tubercle bacilli, only a fraction of the bacilli retained in the alveoli multiply sufficiently to produce grossly visible pulmonary foci. Furthermore, and most significantly, the number of primary tubercles generated is a direct function of the native resistance of the animal (8). The greater the resistance, the fewer the tubercles generated, so that each race is characterized by a certain ratio between the number of bacilli inhaled and the number of primary pulmonary foci. Thus in the most susceptible race C one of 50 inhaled bacilli generates a tubercle; in the somewhat more resistant race FC about 100 are required; while in the most resistant race III only one of 600 inhaled bacilli yields a pulmonary tubercle.

Now by the use of this method it was found that cortisone in pharmacologic doses affects in a fundamental fashion all the essential mechanisms involved in the pathogenesis of tuberculosis. It greatly increases the number of tubercles generated by the inhalation of a given number of tubercle bacilli in a given race of constant genetic resistance. This is achieved by favoring the growth of the bacilli within the phagocytes. It suppresses nonspecific and allergic inflammation by virtue of the protective effect exerted by the hormone against agents which increase capillary permeability. As a result, the tubercles are greatly reduced in size by the suppression of their perifocal inflammation. This antiphlogistic influence, by suppressing the migration and ingrowth of cells and capillaries into the tubercles and by diminishing the communications between the focus and the rest of the body, tends to partially isolate the lesion and localize it at the portal of entry. The reduced capillary permeability and the lympholytic effects of the hormone may also be instrumental in the retardation of development of the caseous process and the diminution of antibody production which is characteristic of the cortisone-treated animals. For allergic sensitization, of which caseation is a part, has now been demonstrated to be at least partially mediated by antibodies. It is noteworthy that some of the effects of cortisone are similar to those of estrogen discussed above.

Thus an excess of the natural cortical hormone markedly influences native resistance to tuberculosis and acts as a double-edged sword. The very suppression of the inflammation, while it tends to isolate the infection from the rest of the body, nevertheless permits the local multiplication of the bacteria. For the phagocytes and the humoral agents concerned with combatting the infection arrive tardily and in low concentration. Furthermore, there is general agreement that cortisone administered during the course of immunization tends to lower antibody production which would also militate against the host. Again, while there is ample evidence that increased adreno-cortical function and cortisone stimulate phagocytosis of particulate matter and bac-

teria, the digestive capacity of the cells for the ingested microorganisms is markedly reduced whether these be tubercle bacilli, pneumococci, streptococci or even red blood cells. Hence, the bacteria can accumulate in the tissues in the absence of allergic inflammation or toxemia which are suppressed by the hormone.

The very fact that an excess of cortisone affects native resistance fundamentally both favorably and unfavorably would suggest that a proper balance between the adrenal and other hormones of internal secretion might exert entirely beneficial influences on this process. Indeed, experiments with minimal effective doses of ACTH, suggest that the resistance of certain inbred animals of low native adrenal function can be increased by corticotropin. Similar treatment of rabbits with higher genetic adrenal function has no effect. These observations were made in races FC and C, respectively. Furthermore, even in the FC race which is characterized by the low native adrenal function, the beneficial effects from ACTH, i.e., the reduction in the number of primary pulmonary foci generated by the inhalation of a given number of human type tubercle bacilli, can be obtained only within very narrow limits. A slight excess of ACTH may induce effects due to excessive secretion of cortisone-like hormones as suggested by a tendency for an increase in the number of tubercles generated by a given number of inhaled bacilli and by a constant diminution in the size of the primary pulmonary foci.

Thus genetic resistance to tuberculosis in different rabbit races is determined essentially by their varying native capacities to retard the initial growth of the bacilli within the phagocytes that ingest the microorganism and their subsequent varying innate ability to develop rapidly and intensely an increased power to destroy or inhibit the multiplication of bacteria. It is noteworthy that the intensity of this acquired resistance developed during the course of the infection tended to be superimposed on and determined by the native initial capacity possessed by a given race to retard the growth of the bacilli. This generalization applies to the resistance of these races to both mammalian bacilli, human and bovine; but it is particularly evident in the native resistance of these races to the human type bacillus to which the rabbit, as a species, is much more resistant than to the bovine tubercle bacillus.

The analysis of the pathogenesis of the disease in the different races suggests that the factors which determine resistance are multiple, and that no one single factor is invariably associated with resistance or susceptibility. Thus low connective tissue permeability and a high rate and intensity of development of allergic sensitivity and antibodies tend to be associated with resistance, but not invariably so. The sex hormones thus far studied exert opposite effects on the dissemination of the disease, but they do not affect the essential process of resistance, which is the rate of growth and destruction of tubercle bacilli in the tissues. There is some parallelism between adrenal size and native resistance,

but again not uniformly so. The adreno-cortical hormone, cortisone, exercises profound influences on the resistance to the disease, but these are not all in the same direction. Minute doses of ACTH can raise the resistance of certain races, but affect the resistance of other races not at all. Furthermore, even in the same race, corticotropin in slight excess may have an opposite effect.

INHERITANCE OF NATIVE RESISTANCE

It is clear even from the limited observations thus far made on the role played by some hormones in resistance to the disease, that the determinants of this genetic resistance are numerous, complex and interacting. In fact, the work of Wright and Lewis (12), Webster (11), Irwin (3) and Gowen (2) suggest that the factors involved in the inheritance of resistance to a number of infections are multiple and complex and that individual resistance cannot be explained according to a simple Mendelian formula. With the development of the method of assaying native resistance by the procedure of quantitative inhalation outlined above, an opportunity arose to ascertain the mode of inheritance of resistance to tuberculosis more rapidly and with more quantitative precision than was possible heretofore.

For this purpose two races were chosen, the highly resistant race III and the highly susceptible race C. When these two races are given a single intracutaneous inoculation of virulent, bovine type tubercle bacilli, race III dies of a slowly progressive ulcerative pulmonary phthisis, the C rabbits die of an acute massive nodular caseous pneumonia and generalized tuberculosis. The duration of the disease in the race III rabbits is about 2 to 3 times that of the C rabbits.

When these two races inhale human type virulent tubercle bacilli, H37Rv, quantitatively and simultaneously, many more tubercles are generated in the susceptible than in the resident rabbits when killed 4 to 5 weeks after inhalation. In race C, on the average, one primary pulmonary focus results from the inhalation of about 50 tubercle bacilli; in race III, over 600 isolated microorganisms, calculated as inhaled, are required to generate a single tubercle (Fig. 1).

As can be seen from Chart I, the log of the ratio between the number of bacilli inhaled and the number of tubercles generated in 14 rabbits of the C race ranged between 1.1 and 2.5 with a mean of 1.7 ± 0.09 and an arithmetic mean of 48 ± 10. It is noteworthy that in 9 of these 14 rabbits the log of this ratio was 1.6 to 1.8 and, in arithmetic terms, from 38 to 66 inhaled tubercle bacilli sufficed to generate a tubercle. As is evident, race C is a rather uniform strain in which the individual resistance, as measured by this method, varies within relatively narrow limits.

In 16 resistant race III rabbits the log of this ratio ranged between 1.9 and 3.6 with a mean of 2.8 ± 0.11 and an arithmetic mean of 640 ± 170 inhaled

tubercle bacilli for each tubercle formed. Clearly the range of individual variation in resistance in race III is far greater than that of C. Nevertheless, the "P" value of the difference between the means of these two races is 0.000 and statistically highly significant.

FIG. 1. The lungs of resistant rabbit III 4=68 and of susceptible rabbit C 12=2, 5 weeks after the simultaneous exposure to an estimated number of 981 and 1081 tubercle bacilli, respectively. Two tubercles were found in the resistant animal and 50 were counted in the susceptible rabbit. The ratio between the number of bacilli inhaled and the number of tubercles generated was 459 for the race III rabbit and 22 for the susceptible C rabbit.

When these two races were crossed, the average resistance of 13 rabbits of the F_1 generation was intermediate between these two extremes. The mean log of the ratio between the number of bacilli inhaled and the number of tubercles generated was 2.5 $\pm$ 0.09 with an arithmetic mean of 340 $\pm$ 84. This ratio is almost exactly half way between the 48 bacilli necessary for the susceptible

race C and the 640 required for the resistant race III in order to generate a single pulmonary tubercle in each, respectively. It is noteworthy that the spread of variation of the individual resistance of the F_1 generation of this hybrid is less than that of either parent strain. Clearly, therefore, the determinants for resistance are certainly not purely dominant or recessive Mendelian factors, but additive in nature. Statistically, the mean resistance of the hybrid IIIC is significantly different from the mean resistance of either the C or the III race; the "P" value of this difference in the first instance is 0.000 and in the second instance it is 0.03.

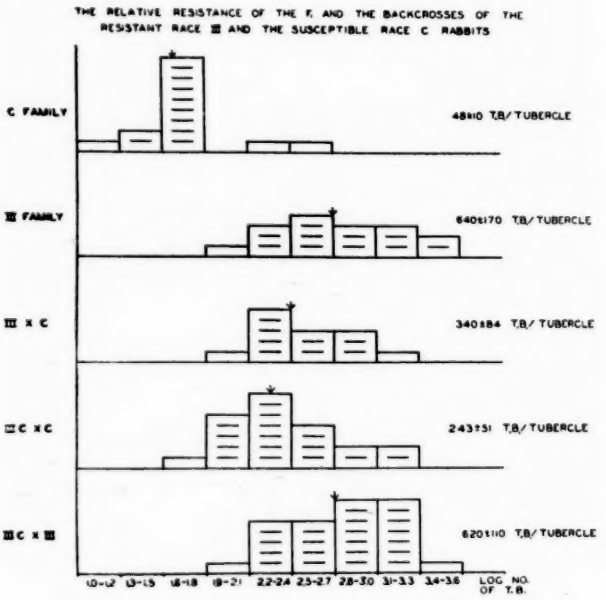
THE RELATIVE RESISTANCE OF THE F, AND THE BACKCROSSES OF THE RESISTANT RACE III AND THE SUSCEPTIBLE RACE C RABBITS
C FAMILY
48±10 T.B./ TUBERCLE
III FAMILY
640±170 T.B./ TUBERCLE
III x C
340±84 T.B./ TUBERCLE
III C x C
243±51 T.B./ TUBERCLE
III C x III
620±110 T.B./ TUBERCLE
10-12 13-15 16-18 19-21 22-24 25-27 28-30 31-33 34-36
LOG NO. OF T.B.

CHART I

When this hybrid IIIC is back-crossed to the susceptible race C there is a clear tendency for many of the individual animals of this back-cross to approach in their resistance that characteristic of the susceptible strain C so that on the average fewer tubercle bacilli are required to generate a tubercle in this back-cross than in the F_1 hybrid. The log of the mean ratio between the bacilli inhaled and the tubercles generated is 2.4 ± 0.09 instead of 2.5 ± 0.09 and the arithmetic mean is 243 ± 51 for this back-cross instead of 340 ± 84 which was the number of bacilli required to generate a single tubercle in the F_1 IIIC. Although 21 rabbits of the IIIC X C cross were studied, the range of variation in resistance was so great, from a log of 1.7 to 3.2, that the mean

resistance of IIIC was not significantly different from that of IIIC X C. However, the mean resistance of the IIIC X C was significantly different from that of races C and III.

When this hybrid IIIC was back-crossed to the original highly resistant race III, both the mean resistance and the range of individual resistance was

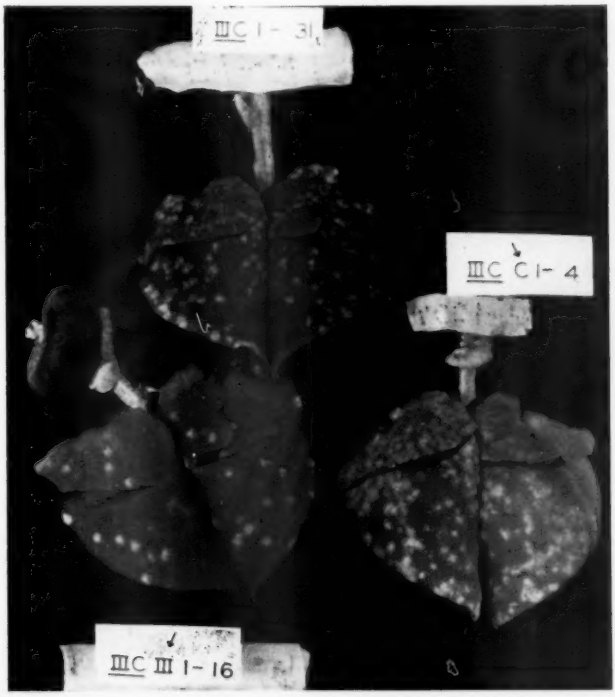

FIG. 2. The lungs of an F_1 hybrid, IIIC 1-31, of a back-cross of the F_1 hybrid to a resistant ancestor, IIICIII 1–16, and of a back-cross of the F_1 hybrid to a susceptible ancestor, IIICC 1–4, 4 weeks after the simultaneous exposure to an estimated number of 75,028, 79,171 and 63,521 tubercle bacilli, respectively. 497 tubercles were found in the F_1 hybrid; 142 tubercles were counted in the F_1 hybrid back-crossed to the resistant ancestor; and 772 tubercles were estimated to be present in the F_1 hybrid back-crossed to the susceptible ancestor. The ratio between the number of bacilli inhaled and the number of tubercles generated was 131 for the F_1 hybrid, 557 for the back-cross to the resistant ancestor and 82 for the back-cross to the susceptible ancestor.

practically identical to that of the highly resistant parent race III. The log of the mean number of bacilli required to generate a primary pulmonary focus in this cross was 2.8 ± 0.08 and an arithmetic mean of 620 ± 110 which is essentially the same as these values for race III, namely, 2.8 ± 0.11 and 640 ± 170. Obviously the difference between these figures is not significant. Furthermore, the range of individual variation in resistance in this back-cross

IIIC X III is also essentially the same as the range in the parent race III, log 1.9 to 3.6 in IIIC X III and 1.9 to 3.6 in race III. The relative resistance of the F_1 hybrid and the two back-crosses is illustrated in Fig. 2. Since the back-cross IIIC X III is of the same resistance as the original resistant race III ancestors, it would follow that the resistance of this back-cross is significantly different from that of races C, IIIC and IIIC X C as in case of race III. This was found to be the case.

It is imperative to state that exactly the same relationships held between the relative resistance of these races, the F_1 hybrids and the back-crosses, when all the data were evaluated in their originally observed arithmetic terms.

Thus the back-cross of IIIC to the resistant ancestor III is as resistant as the original race III. However, the back-cross of the same hybrid IIIC to the susceptible ancestor C is much more resistant than the original race C. For the mean resistance of IIIC X C is significantly much higher than that of the C race. These data would suggest that not only are the determinants for resistance multiple, but also that the factors for resistance are either more dominant in the phenotype than determinants for susceptibility, or that susceptible individuals lack certain qualities which resistant animals possess. These results do not prove either of these concepts. If this apparent phenotypic dominance of resistance holds in man, it is understandable why the mortality from tuberculosis may slowly diminish during the course of generations in an actively interbreeding society of heterogeneous native resistance apart from the forces of natural selection and hygienic measures taken. No light is shed by these observations on the number or dominance of the genes concerned with the inheritance of resistance, except that they are multiple and additive in nature. Whether a deeper understanding of the mode of inheritance of resistance in tuberculosis can be obtained from ascertaining the resistance of larger numbers of individuals of the various crosses presented thus far and from the F_2 generation of the IIIC hybrid is uncertain.

SUMMARY

An analysis of the pathogenesis of tuberculosis induced in inbred rabbit races of different genetic resistance to the disease by various methods of inoculation of bovine, human and attenuated tubercle bacilli has demonstrated that native resistance to tuberculosis in the rabbit is determined by the innate varying capacity of the phagocytes that ingest the microorganism to inhibit their intracellular multiplication, initially, and by their varying inborn aptitudes to develop rapidly and effectively an increased power to destroy the microorganism after the onset of the infection. The resistance acquired by a given race during the course of a given infection or after a certain immunization is greater in the natively resistant than in the natively susceptible strains.

High native resistance is often but not always associated with a low connective tissue permeability, and, more commonly, with a high level of develop-

ment of allergic sensitivity and antibodies. Estrogen, by reducing the connective tissue and vascular permeability, retards the dissemination of the disease and prolongs its course. Gonadotropin enhances the spread of the disease and shortens its duration by increasing connective tissue and vascular permeability. Neither hormone influences the growth and destruction of tubercle bacilli in the tissues, antibody production or the essential nature of the development of allergic sensitivity.

There is an incomplete parallelism between native resistance and adrenocortical function as indicated by its mass in relation to body weight. Cortisone in pharmacologic doses reduces the innate capacity of the phagocytes to destroy the ingested bacilli. It suppresses nonspecific and allergic inflammation as a result of the protective effect exercised by the hormone on the capillary walls against agents which increase their permeability. Cortisone tends to temporarily localize the disease at the portal of entry because the hormone suppresses inflammation and consequently reduces the cellular and humoral bridges between the focus and the rest of the body. Withdrawal of the hormone greatly accentuates the inflammation and the bacilli, accumulated in the foci as a result of a paralysis of the cellular digestive capacities by cortisone, now spread widely in the tissues and may cause a fatal issue in an animal which without this usually arrests the disease. Minimal doses of ACTH increased the resistance of rabbits with low native adrenal function but had no effect on a race with natively large adrenal cortices.

The most accurate, quantitative and rapid method of ascertaining native resistance, thus far, is the one of exposing animals to the quantitative inhalation of human type tubercle bacilli, to which this species is relatively resistant, and of determining the number of grossly visible primary pulmonary tubercles generated in them 4 to 5 weeks after this infection. The greater the native resistance, the fewer are the tubercles formed after the inhalation of a given number of microorganisms.

By the use of this method, the determinants of native resistance were found to be multiple, complex and additive in nature. The resistance of the F_1 hybrids of a natively highly resistant and highly susceptible race was intermediate between that of each parent race. The back-cross of the F_1 hybrid generation to the resistant ancestors yielded a strain which was of the same degree of high resistance as the original resistant race. The back-cross of the F_1 hybrids to the susceptible ancestors was significantly more resistant than the original susceptible ancestors. Phenotypic dominance of resistance over susceptibility is a possible, but not the only, interpretation of the observations. The implication of these data for the epidemiology of human tuberculosis is briefly discussed.

REFERENCES

1. Brown, J. H., Cook, K. M., Ney, F. G. and Hatch, T. 1950. Influence of particle size upon the retention of particulate matter in the human lung. *Am. J. Pub. Health.*

40: 450–458; GOLDBERG, L. J. AND LEIF, W. R. 1950. The use of radioactive isotopes in determining the retention and initial distribution of airbone bacteria in the mouse. *Science*, 112: 299–300; SONKIN, L. S. 1951. The role of particle size in experimental airborne infection. *Am. J. Pub. Health.* 53: 337–354.

2. GOWEN, J. W. AND CALHOUN, M. L. 1943. Factors affecting genetic resistance of mice to mouse typhoid. *J. Infect. Dis.* 73: 40–56.
3. IRWIN, M. R. 1929. The inheritance of resistance to the Danysz bacillus in the rat. *Genetics.* 14: 337–365.
4. LURIE, M. B. 1941. Heredity, constitution and tuberculosis, an experimental study. *Amer. Rev. Tuberc.* 44: No. 3, suppl. 1–125.
5. LURIE, M. B., ABRAMSON, S., HARRIS, T. N., ALLISON, M. J. AND HEPPLESTON, A. G. 1949. Constitutional factors in resistance to infection. I, II and III. *Am. Rev. Tuberc.* 59: 168–185, 186–197, 198–218.
6. LURIE, M. B., HEPPLESTON, A. G., ABRAMSON, S. AND SWARTZ, I. B. 1950. An evaluation of the method of quantitative airborne infection and its use in the study of the pathogenesis of tuberculosis. *Am. Rev. Tuberc.* 61: 765–797.
7. LURIE, M. B., ZAPPASODI, P., DANNENBERG, A. M., JR. AND SWARTZ, I. B. 1951. Constitutional factors in resistance to infection. The effect of cortisone on the pathogenesis of tuberculosis. *Science.* 113: 234–237.
8. LURIE, M. B., ABRAMSON, S. AND HEPPLESTON, A. G. 1952. On the response of genetically resistant and susceptible rabbits to the quantitative inhalation of human type tubercle bacilli and the nature of resistance to tuberculosis. *J. Exp. Med.* 95: 119–134.
9. LURIE, M. B., ZAPPASODI, P., CARDONA-LYNCH, E. AND DANNENBERG, A. M., JR. 1952. The response to the intracutaneous inoculation of BCG as an index of native resistance to tuberculosis. *J. Immunol.* 68: 369–387.
10. LURIE, M. B., ZAPPASODI, P., DANNENBERG, A. M., JR. AND CARDONA-LYNCH, E. 1952. Constitutional factors in resistance to infection. The effect of cortisone on the pathogenesis of tuberculosis. *Symposium on the Effect of ACTH and Cortisone Upon Infection and Resistance.* Columbia University Press. (in press)
11. WEBSTER, L. T. 1933. Inherited and acquired factors in resistance to infection. *J. Exp. Med.* 57: 793–817.
12. WRIGHT, S. AND LEWIS, P. A. 1921. Factors in the resistance of guinea pigs to tuberculosis, with special regard to inbreeding and heredity. *Am. Naturalist.* 55: 20–50.

4. The Bearing of Mouse Genetics on Our Understanding of Human Cancer[1]

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THE problems involved in our understanding of the cause, origin and development of cancer are basically problems in biology. The study of neoplasia concerns living cells and the factors acting through the physiology of the living

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organism and of the cell to cause it to take on a new characteristic of uncontrolled growth and to support this growth. Cell differentiation, cell nutrition, growth and biochemistry are involved, and, in that all of these are under the control of the genotype of the organism and of the cell, genetics is likewise involved. It is, therefore, through studies in genetics that much of our fundamental understanding of cancer is derived.

Because of difficulties in the collection and analysis of data from human beings on such a complex character as cancer, the ground work for the study of the genetics of cancer must be done with some other species. Important contributions to our understanding of the problem have been made and will continue to be made by investigations with Drosophila, corn, Neurospora and other lower organisms. Because of its physiology approximating that of man and because of its wide variety of neoplasms occurring with such frequency necessary for adequate study, the mouse, however, has provided the most extensive approach to the problem. Certain superficial facts revealed obviously can be applied only to the mouse, but basic facts and concepts derived from studies on the mouse can also be applied to man.

IS CANCER INHERITED?

From genetic studies in mice one is forced to conclude that probably every type of cancer in man can be subject to genic influence so that under certain conditions the genotype of the individual may be the deciding factor in determining whether or not the individual develops a certain type of cancer. Through the manipulation of genes in the development of the inbred strains, and through hybridization of the strains, geneticists have been able to prevent or promote the occurrence of more different types of cancer and to influence the occurrence of each to a greater degree than has any other investigator with any other group of agents. Strains vary in respect to incidence of mammary gland tumors from strain C3H in which 95 per cent or more of the females have mammary tumors to strain C57 BL in which less than one per cent of the females develop mammary tumors (Andervont, 1941, Heston *et al* 1950). Extremes in regard to pulmonary tumors are strain A with an incidence of 90 per cent at 18 months of age and strain C57 L in which only 3 spontaneous pulmonary tumors have been observed in the thousands of mice throughout the history of the strain (Heston, 1942b). Strains C58, and AKR are known for their high incidences of lymphocytic leukemia. (MacDowell, *et al.* 1945, Law, 1948). These have been reported as high as 90 per cent. Little (1941) has reported an incidence of non-epithelial tumors of about 20 per cent in strain C57 BL. Most of these were classified as lymphoblastomas. About 25 per cent of mice of strain C57 L develop a Hodgkins-like lesion. In contrast, in strains A and C3H neoplasms of the blood-forming organs are rarely found. Hepatomas occur in approximately 30 per cent of strain C3H males and 10 per cent of the females

(Andervont 1941). Strong (1945) has developed a strain with a high incidence of tumors of the glandular stomach, and strain I has a high incidence of a lesion of the glandular stomach (Andervont and Stewart, 1937), whereas tumors of the gastrointestinal tract rarely occur in other strains. Pybus and Miller (1938) reported a strain of mice with a high incidence of bone tumors, a type rarely found in other strains. Gardner and Pan (1948) reported a strain PM derived from the original Pybus and Miller strain with a high incidence of spontaneous uterine, cervical and vaginal tumors, although none were observed in 6 other strains. Woolley and co-workers (1945) developed a strain CE with a high incidence of carcinoma of the adrenals following early castration. With the same treatment strain DBA mice showed only hyperplasia of the adrenal cortex and strain C57 BL mice gave little if any adrenal response. Burdette and Strong (1943) reported genetic differences in the incidence of subcutaneous sarcomas following the injection of methylcholanthrene. Strain $C3H_f$ mice without the milk agent and their hybrid derivatives have a higher incidence of spontaneous subcutaneous sarcomas than have other strains. Mice of strain HR which carries the hairless gene have a relatively high incidence of spontaneous papillomas and when painted with methylcholanthrene develop a higher incidence of squamous-cell carcinomas than has been reported for any other strain (Deringer, 1951). Even in respect to very rare tumors such differences are seen. Myoepitheliomas, often of salivary gland origin, occur much more frequently in strain A than in any other strain. In hybrids between strains C3H and C57 BL a number of tumors of the Harderian gland were noted although this tumor has not been reported in any inbred strain or other type of hybrid.

From these observations of genetic differences in respect to these many varied types of tumors it is safe to assume that strains of mice differing in incidence of any type of tumor could be developed with the proper genes in the original population followed by the necessary selection.

One who has worked with these strains of mice, therefore, no longer asks if cancer is inhreited in man. Instead he asks how is cancer inherited in man and how important are the genetic factors as compared with the various non-genetic factors in determining whether or not cancer will occur.

CAN A GENERAL INHERITED SUSCEPTIBILITY TO CANCER IN MAN BE EXPECTED?

One of the first questions to be answered by data from the inbred strains is whether or not a general susceptibility to cancer is inherited. The fact that the strains are susceptible to specific types of cancer and that almost no strain is resistant to all types has indicated that the various types are inherited as independent characteristics. For the most part this would be expected when one visualizes the physiologic paths through which the genic action must become manifest. It is difficult to perceive how the development of pulmonary

tumors could be preceded by the same physiologic factors that affect mammary gland tumor development.

On the other hand it would seem possible that the development of tumors in different organs of the same physiological system might have a common genetic basis. Variations in hormonal balance might influence tumor development in a number of endocrine organs, the reproductive organs and the breast. There is some evidence of a relationship between adrenal hyperplasia and the genes influencing mammary tumors through the control of the hormonal stimulation in mice. (Smith 1948, Huseby and Bittner 1948). Data of Macklin (1952) suggest that such an association may be demonstrated in man in the relationship between breast cancer and cancer of the prostate. In the mouse specific genes have been shown to influence the development of more than one tumor, but, as will be discussed subsequently, the effect may be through separate physiologic paths and one gene may have opposite effects upon two different types of tumor.

MULTIPLE FACTOR INHERITANCE OF CANCER

Another major question to be answered is in regard to the type of inheritance observed in respect to cancer. It should be emphasized that in studies of the mouse where breeding experiments can be carried out and where F_2 and backcross segregants can be tested to differentiate between single factor ratios and simulated single factor ratios due to fluctuations about physiologic thresholds, not one type of cancer has thus far been shown to be controlled by a single gene. This would demand caution in concluding single factor inheritance for cancer in man. Before inbred strains of mice were available and when the only estimate of the genotype was the observation of whether or not the individual mouse developed a tumor, results were obtained which were interpreted as indicating single factor recessive inheritance. Following the development of the inbred strains single factor dominant inheritance was indicated by certain simple crosses. This was true of both pulmonary tumors and mammary gland tumors in mice. The variation between the various inbred strains, however, could not be explained with such simple interpretations. For example, in regard to pulmonary tumors, strain A has an incidence of 90 per cent, strain Swiss 40 per cent, strain BALB/c 20 per cent, strain C3H between 5 and 10 per cent and C57 L and C57 BL less than one per cent. Furthermore, when strain A was outcrossed to three different low-tumor strains the degrees of susceptibility to induced pulmonary tumors observed in the three resultant groups of F_1 hybrids were not the same but were relatively high, medium and low (Heston, 1940). Later by utilizing the number of nodules appearing in the lungs of each individual as a reliable quantitative measure of degree of susceptibility to induced pulmonary tumors and checking these results against those obtained by using latent period as a measure of susceptibility multiple factor inheritance

was established for induced pulmonary tumors (Heston, 1942a). Through hybridization studies multiple factor inheritance has also been established for spontaneous pulmonary tumors (Heston, 1942b). Here, as with the genetic analysis of other spontaneous tumors, there is not a quantitative measure of degree of susceptibility and the problem is more comparable to that of polydactyly in the guinea pig described by Wright, (1934b), i.e. that of a multiple factor character with alternative expression depending upon whether or not the combined action of the genetic and non-genetic factors surpasses a physiologic threshold.

While a quantitative measure of degree of susceptibility to mammary gland tumors in mice has not been available, the vast amount of data on mammary tumors, both from tabulation of incidences in the various strains and from hybridization studies, can be explained only on the basis of multiple factors (Bittner, 1952, Heston, 1945). Burdette (1943) has demonstrated multiple factor inheritance for induced subcutaneous sarcomas, and since the F_1's were intermediate he assumed that at least one factor was dominant and one was recessive. In crosses between high and low leukemic strains Cole and Furth (1941) observed that the incidence of leukemia in the hybrid groups was roughly correlated with the total heredity from the high leukemic strain. Through breeding tests of backcross segregants MacDowell *et al* (1945) established the inheritance of leukemia as multiple factor. Data on other types of tumors in mice consists primarily of incidence data of the inbred strains, but none suggests single factor inheritance.

DOMINANCE

In consideration of multiple factor inheritance of cancer in mice with alternative expression resulting from fluctuation of the combined action of genetic and non-genetic factors about physiologic thresholds, one is reluctant to accept the inheritance of a specific type of cancer in mice or in man as dominant or recessive. The early interpretation of recessive inheritance in mice can probably be explained in that the cancers observed were the result of a relatively low genetic influence together with a strong non-genetic influence. Thus, matings of cancer $\times$ non-cancer seldom yielded cancer whereas cancer $\times$ cancer did. The later interpretation of dominant inheritance may be explained in that in the development of the inbred strains such a high level of genetic influence for specific cancers was concentrated in certain strains that even on outcrossing to low-tumor strains the level was not lowered so much but that a majority of the F_1's developed cancer. The F_1's usually lived longer, giving a longer time for the accumulation of non-genetic influences. Much confusion is avoided by reserving the terms "dominant" and "recessive" to be applied when specific genes have been identified.

"LINKAGE"

Associations between specific genes of the mouse and susceptibility to specific types of tumors indicate the value of similar linkage studies in man and suggest possible physiologic paths through which gene action may influence the probability that a specific type of tumor will occur. Strong (1945) has reported linkage between the brown locus and the stomach tumor induced in his BRS strain, although such linkage was not observed for the spontaneous tumors (Strong and Hollander, 1951). Bittner (1945) reported linkage between brown and mammary gland tumors. In two different experiments (Heston and Deringer, 1948) agouti backcross females from a cross between C3H and C57 BL had a higher incidence of mammary tumors than had the non-agouti females, suggesting an effect of the agouti gene. Little (1934) reported an association between lethal yellow an allele of agouti and mammary gland tumors. The tumors came up earlier in the yellow females than in their non-yellow sibs although the final incidence was lower in the yellow females. Manifestation of the primary action of the gene through the physiology of the endrocrine system was indicated. The yellow females became sexually mature earlier but passed through their reproductive period earlier than did the non-yellow females.

Lethal-yellow increases susceptibility to pulmonary tumors (Heston 1942c, Heston and Deringer 1947), but here the association may be related to the effect of the gene on body size. Association with pulmonary tumors has also been demonstrated for shaker-2, hairless and flexed-tail (Heston, 1941, Heston *et al* 1949, 1951, 1952). It has been established that the association with lethal-yellow was due to the gene *per se*, and the evidence available also indicates that the associations with the other three were probably also owing to the genes *per se* rather than to true linkage. In the case of flexed-tail there appeared to be a closer association with the flexed-tail manifestation of the gene than with the anemia. Although not every factor that affects body weight affects susceptibility, e.g. there is a sex difference in weight but no sex difference in susceptibility, there is a suggestion that these genes may be affecting susceptibility to pulmonary tumors through some effect upon growth in general. Lethal yellow increased susceptibility to pulmonary tumors, whereas the other three genes decreased susceptibility, and lethal yellow increased body weight, whereas the other three decreased body weight.

The dilution gene is similarly of interest. Little *et al*, (1934, 1939) reported an association between dilution and an increased incidence in non-epithelial tumors and MacDowell *et al*. (1945) found that dilution increased the occurrence of leukemia. This gene also has been shown by MacArthur (1949) to increase body size. The relationship of all of these genes to neoplastic and normal growth has important implication in respect to life insurance data reviewed by Tannenbaum (1940) as indicating that obese human beings are

more susceptible to cancer than are individuals of more normal weight. It is suggested that this relationship in man may be basically genetic.

Law (1952b) has established a relationship between flexed tail and leukemia, although there was none between leukemia and the linked genes shaker-2 and waved-2. There was no indication here that the effect of the flexed-tail gene upon the occurrence of leukemia was associated with its effect upon body size. The flexed tailed animals were more susceptible to leukemia than were the non-flexed. In this case the association may be related to the anemia manifestation of the gene in that although the mice recover from the anemia within a few days after birth there may be a weakness in the hematopoietic system which later predisposes to leukemia. This association is particularly interesting in view of the reported higher incidence of pernicious anemia among relatives of leukemia patients than among relatives of control probands (Videbaek, 1947), and adds support to the interpretation of a genetic basis for the relationship in man.

LOCALIZATION OF PRIMARY GENE ACTION

More progress has been made in the study of paths through which unidentified genes influence the development of tumors in the mouse than through which the actions of these identified genes become manifest. Although four specific genes have been shown to influence susceptibility to pulmonary tumors, their effects do not constitute the total genetic control of susceptibility. Strain A and strain C57 L which represent the two extremes in genetic susceptibility do not differ by any of these four genes.

Through transplantation studies (Heston and Dunn, 1951) it has been shown that the primary action of at least most of the genes for susceptibility by which these two strains differ is localized in the pulmonary cells rather than becoming manifest through some general systemic mechanism. Transplants of normal pulmonary tissue from both susceptible strain A and resistant strain L were made in a common host, the F_1 hybrid of these strains. Following the intravenous injection of the carcinogen 1:2:5:6-dibenzanthracene into the host, tumors were frequently found in the strain A transplants but rarely found in the strain C57 L transplants. Thus, the tumor response was controlled by the genotype of the transplant and not by the genotype of the host. In a similar study using the Bagg albino strain and strain DBA, Shapiro and Kirschbaum (1951) obtained comparable results.

Caution should be exercised in transposing these findings in the mouse to man especially since pulmonary cancer in man is bronchiogenic in origin whereas that in the mouse is alveolar in origin (Grady and Stewart, 1940, Mostofi and Larsen, 1951). Furthermore, there have been no studies to show that pulmonary cancer in man is inherited. However, studies on the mouse point to the advisability of genetic studies on pulmonary cancer in man, which,

with the reported increased incidence are more feasible now than several decades ago. If gene action is indicated, and experience with the mouse would suggest that it will be with collection of ample data, this action may be limited to the pulmonary cell in man like it is in the mouse.

Much of the genic action controlling mammary tumor development in mice is not localized in the mammary gland cell (Heston, 1946). By crossing susceptible strain C3H having the milk agent with resistant strain C57 BL without the agent and backcrossing the F_1 females to C57 BL males and to C3H males, two groups of backcross females which differed only in their genotypes were produced (Heston, and Andervont, 1945). Both groups had received the milk agent from their genetically identical mothers yet both groups did not transmit the agent the same. When tested by fostering identical test females the susceptible strain backcross females were able to transmit the agent better than were the resistant strain backcross females as indicated by the higher incidence of tumors in the test females for the susceptible strain backcross. The ability to transmit the agent was influenced by the genotype of each backcross group. This conclusion is supported by the fact that the agent dies out in certain resistant strains (Andervont, 1945). Thus, one of the paths through which genes control whether or not mammary gland tumors will occur in mice is through the control of the propagation and transmission of the milk agent.

Another path through which genes control the occurrence of mammary gland tumors in mice is through gene control over the hormonal stimulation. Crosses between strain A in which virgin females rarely develop mammary tumors and strain C3H in which there is a high incidence in the virgins indicated that genes were acting either through the control of hormonal output or the response of the mammary gland to the hormonal stimulation (Bittner, *et al.* 1944, Heston and Andervont, 1944). Studies of estrus cycles revealed little difference between the strains or their hybrids except that those with a high mammary tumor incidence began their cycles at an earlier age (Deringer, *et al.* 1945). Through transplantation of ovaries, however, Huseby and Bittner (1948) have demonstrated that at least some of the genic control is through control of hormonal production. C3H ovaries in F_1 females resulted in a higher mammary tumor incidence than did A ovaries in F_1 females.

This leaves as a third possible gene action path the control of the response of the mammary gland cell to the hormonal or milk agent stimulation by the genes within the cell. More work is needed to differentiate clearly between this path and either of the other two.

Obviously this whole picture cannot be transposed to man. One cannot expect genes to control breast cancer in human beings through control over some extrachromosomal agent until such an agent has been identified. Furthermore, mice and human beings differ in respect to the role of hormonal stimula-

tion in breast cancer. Women who have had children are reported to have a lower incidence of breast cancer than those who have not had children (Wainwright, 1931), the exact opposite to the situation in mice. What is indicated, however, is that in man as well as in mice the inheritance of breast cancer may be very complex with gene action becoming manifest through a number of paths. Attempts to identify such paths are important for it may be found that certain ones will open the way to the application of control measures.

RELATION BETWEEN GENETIC AND NON-GENETIC FACTORS

Much has been done with mice in revealing the additive relationship between genetic and non-genetic factors and the relative importance of each in the development of tumors. The complex situations encountered are difficult to analyze using human material, but general concepts developed from the mouse are helpful in an attempt to visualize the situation in man.

The malignant change represents some permanent change in the cell. As yet we do not know whether basically this is a change in the cytoplasm i.e., a mutation of a plasmagene or some other component of the cytoplasm, or a change in a gene, i.e., a true mutation in the minds of many geneticists. It resembles a mutation in that it is a chance happening the probability of its occurrence being influenced by the intrinsic and extrinsic factors acting upon the organism or the cell. This happening can be compared with the physiologic threshold described by Wright (1934a, and b) in his analysis of polydactyly and otocephaly in the guinea pig.

The additive effect of the genetic and non-genetic factors has been demonstrated most clearly in respect to pulmonary tumors in mice. With the potent genotype of strain A the malignant change has occurred in the lungs of approximately 90 per cent of the animals of this strain by 18 months of age when kept under usual laboratory conditions. As the length of time for this chance happening to occur is shortened the incidence of tumors is decreased, being approximately 50 per cent at 12 months and 20 per cent at 6 months of age. The change usually occurs in only one focus of the lung giving rise to a single nodule, although there may be two or three but rarely more. Following the intravenous injection of .5 mg. 1,2,5,6-dibenzanthracene, a potent carcinogen, pulmonary tumors occur in 100 per cent of the mice of this strain within 6 weeks and by 4 months the change will have occurred in about 75 foci for there will be on the average 75 nodules. As time increases the number of nodules increases until because of coalescing they no longer can be counted.

Strain C57 L is genetically very resistant to pulmonary tumors. In the history of the strain the malignant change has been observed to occur only 3 times in the lungs of these mice kept under usual laboratory conditions. When strain C57 L mice were injected with the same carcinogen as were the strain A mice the incidence of tumors was raised to only 24 per cent and this incidence

was attained only after keeping the animals for 12 months. Furthermore, most of the animals had but a single nodule.

Strain BALB/c can be cited as one with an intermediate genetic potency. Pulmonary tumors occur in about 20 per cent of the mice of this strain kept under usual laboratory environment. When injected intravenously with .5 mg. dibenzanthracene the malignant change occurred in the lungs of all mice by 5 months but instead of the extremely high number of nodules such as found in strain A mice there was an average of only 10 nodules.

Much other data could be cited to demonstrate further that following the introduction of a carcinogen of uniform dosage, the strains, although all showing an increased pulmonary tumor response, retain their relative positions observed for spontaneous tumors. These carcinogens include a host of compounds including polycyclic hydrocarbons, urethane (Nettleship and Henshaw, 1943) and nitrogen and sulfur mustard (Heston, 1949, 1950). Radiation also increases the occurrence of pulmonary tumors in mice (Lorenz *et al.* 1946). This was first demonstrated with strain A which has a potent genetic influence, but later a significant although less effect was noted in LAF_1 animals which have a less potent genetic influence.

Not all influencing factors, however, add to the pulmonary tumor response. Strain A mice fed a low-calorie diet had fewer tumors than did the controls (Larsen and Heston, 1945).

The concept illustrated here should be kept in mind when attempting to visualize the relative importance of different factors influencing the occurrence of cancer in man. It is to be expected that tumor response of human beings to radiation or other possible industrial agents may likewise be governed in large measure by the genotype of the individual. Because of the great genetic variation of the human population, great variation in response to these possible exogeneous agents may be expected. The inhalation of small amounts of radon by the miners of Schneeberg and Joachimsthal over a long period of time has been suggested as the explanation of the fact that approximately 50 per cent of them died of pulmonary cancer. Before generalizing on the possible effect of radon in causing pulmonary cancer from observations on these isolated communities it is, of course, necessary to investigate the possibility of there having been inbreeding or other patterns of marriages which may have concentrated in these communities genetic factors that may have contributed in large measure to the high incidence of pulmonary cancer.

Mammary gland tumors in mice are inherited in the same general pattern as are pulmonary tumors in that there are multiple genetic and non-genetic factors each of which can influence the probability that the tumor will occur. No factor can be considered as the cause of the mammary tumor but each is to be viewed in respect to its effect upon this probability. This effect can be measured accurately only when all other factors are controlled. The situation

in respect to mammary tumors is more complex than that in respect to pulmonary tumors, for, among the non-genetic factors, there are not only the exogeneous factors such as the chemical carcinogens and radiation, but there are also the endogeneous factors including the milk agent and the hormonal stimulation which are intimately related to the genotype.

The discovery of the extrachromosomal factor in the etiology of mammary cancer in mice by the staff of the Roscoe B. Jackson Memorial Laboratory (1933) and by Korteweg (1934), and the subsequent identification of this factor as a milk agent by Bittner (1936), has had an important bearing upon the cancer problem in man. However, the value of these observations was not as a basis for recommending that mothers not nurse their female babies. Failure of Macklin (1952) in her studies to demonstrate a milk agent in respect to human breast cancer has emphasized the rashness of such a recommendation. The principal value was as a basis for the suggestion of a possible extrachromosomal agent in man and the necessity of work to reveal such an agent if it were present. The dependence of the milk agent upon a suitable genotype has also been of significance in planning investigations with human cancer. It should be emphasized that the agent was revealed through genetic techniques and only after genetically controlled strains were established. Furthermore, the fact that it is transmitted early in the life of the mouse is also of significance. It is to be expected that if there is a virus associated with breast cancer, or any other cancer in man, it may well be revealed through genetic studies in which attention is not only focused upon the individual at the time the cancer occurs, but also throughout his early life and throughout the life of his relatives.

One of the more recent developments in investigations of mammary tumors in mice has been in respect to tumors that occur in the absence of the milk agent (Kirschbaum, 1949, Andervont and Dunn, 1950, Heston, *et al.* 1950). In certain strains the application of carcinogens is required to bring out a large number of these tumors, but in strain $C3H_f$ ($C3H_b$) an incidence of 38 per cent was observed in untreated females. It was necessary, however, that these $C3H_f$ females have many litters in order to have such a high incidence of tumors. The incidence in virgin $C3H_f$ females was less than 5 per cent. A longer latent period was also needed for the tumors to appear. The average tumor age for the $C3H_f$ breeding females was 20 months whereas the tumors occur at an average age of 8 months in the C3H females with the agent.

There was a higher frequency of unusual histologic types among these tumors occurring in the absence of the agent. Tumors with squamous metaplasia classified as adenocanthomas, those with dilated alveolae with muscle elements in the aboundant stroma that Dunn (In Press) has designated as type C, and those with sarcomatous elements classified as carcinosarcomas, occurred relatively frequently in animals without the agent. Tumors arising in females with the agent usually show uniform ascinar structure, i.e., Dunn's type A, or the

cells occur in cords or sheets, i.e., Dunn's type B, whereas the other histologic types occur rarely in the presence of the agent. This variation may, however, be a more direct expression of tumor age rather than presence or absence of the agent.

Biologically these tumors that arise in the absence of the agent may be more comparable with human breast cancer than are those arising with the agent, and a more thorough study of them may reveal further suggestions applicable to human studies. In reciprocal outcrossing of strain $C3H_f$ with low-tumor strain C57 BL (Heston and Deringer, 1952) no maternal influence of any kind was revealed in that there was no difference in tumor incidence of the reciprocal hybrids. This would suggest that the difference between the two parent strains was for the most part genetic, and, since the incidence of tumors in the F_1 groups was intermediate, at least one dominant gene and one recessive gene, or no dominance, was indicated.

These studies do not detract from the importance of the milk agent. One must bear in mind that these $C3H_f$ females, which will have an incidence of mammary tumors of 38 per cent at 20 months in the absence of the milk agent, will have an incidence of 95 per cent at 8 months if they receive the milk agent when nursing. These studies, however, do throw a somewhat different light on the problem of viruses than has often been viewed in the past, and this may be of importance in the human cancer problem. The mammary tumor disease in mice can no longer be looked upon as a virus disease, such as small pox, in which the individual gets the disease only when he gets the virus. It must be considered as a disease the frequency of which can be greatly enhanced by the introduction of a virus, but which may also occur in indistinguishable form in the absence of the virus. The same situation may prevail in man even if a virus is identified in the etiology of human cancer.

SOMATIC MUTATION HYPOTHESIS

Work with the mouse in testing the somatic mutation hypothesis of cancer can have direct bearing upon our understanding of human cancer. If this hypothesis is proved for mice or any other species it should apply to all, including man. Until new techniques are developed and adapted to the detection of gene changes in somatic tissue, support of the hypothesis will have to rest largely upon indirect evidence.

One of the approaches to the problem has been through a search for a positive correlation between carcinogenic and mutagenic potencies of compounds. While the mouse is an excellent animal for carcinogenic studies, it presents certain difficulties in mutagenic studies. The development of the chromosomal map of the mouse, however, is helping to alleviate such difficulties. Strong (1949) has reported mutations in mice induced by subcutaneous injection of 20-methylcholanthrene, one of our most potent carcinogens, and Carr (1948)

also reported mutations in mice induced with the same compound. Unfortunately in both projects the mutations were observed in hybrids, and critical controls were lacking, but both reports are of importance and emphasize the necessity of further testing with controlled stocks. Nitrogen mustard and sulfur mustard which are strong mutagens when tested on Drosophila and other lower organisms (Auerbach, 1949) both have been shown to be potent carcinogens when injected into mice and rats (Boyland and Horning, 1949, Griffin, et al., 1950, Heston, 1949, 1950). On the other hand, mustard oil that Auerbach found to be a weak mutagen, did not increase the occurrence of tumors in a detectable amount. Thus, there appears to be a positive correlation between carcinogenesis and mutagenesis from the work done in mice. It should be pointed out, however, that Burdette (1950) has not found such a correlation in Drosophila. Furthermore, radiation, which when added to nitrogen mustard has an additive effect in inducing mutations in Drosophila, when added to nitrogen mustard in mice has a diminishing effect on carcinogenesis. (Heston, *et al*, unpublished data.)

Other information bearing on this problem has been obtained through dose-response analysis. In an analysis of the number of papillomas arising in mice painted semi-weekly with benzpyrene, Charles and Luce-Clausen (1942) found a straight line relationship when the square-root of the number of papillomas was plotted against time, and expression of dose. This would be expected if the malignant change were the result of two events in the cell, i.e. if the malignant change were the result of a recessive mutation. However, in an analysis of the number of pulmonary tumors occurring in mice injected intravenously with graded doses of dibenzanthracene (Heston and Schneiderman, In Press) a straight line relationship was observed when the number of tumors was plotted against the dose. This result would be expected if the malignant change were dependent upon a single happening in the cell, i.e. a dominant mutation.

While these approaches have not succeeded in proving or disproving the somatic mutation hypothesis they do illustrate how the mouse can be adapted to a search for the answer to this question. When obtained this answer will apply to cancer in man as well as in the mouse. It should be emphasized that proof of the hypothesis would not eliminate any possibility of preventative measures against cancer. The fact remains that there are many factors that increase the probability that this change occurs even though the change may be a mutation. The elimination of each of these factors would decrease to a certain degree the probability of the occurrence of the cancer.

PROBLEMS IN THERAPY

Aside from contributing to our understanding of problems in the development of cancer in man, genetic studies in mice also have been used to clarify problems in the treatment of human cancer. One of the greatest difficulties arising

in the chemotherapy of human cancer, specifically leukemia, has been the development of resistance of the leukemia cells to the drug during the course of treatment. The question arises as to what is the nature of this resistance.

Fortunately the mouse provides an experimental approach to the problem for transplantable mouse leukemias respond to the same chemotherapeutic agents that are effective against human leukemia. Law (1951, 1952a) particularly has studied resistance of transplantable mouse leukemia to folic acid antagonists and has employed techniques similar to those used in the analysis of resistance of bacteria to antibiotics. He has found that through the course of treatment certain strains of leukemia arise which can tolerate the antifolic compounds. Furthermore, some strains were shown later to develop a dependence upon the compounds just as bacteria may develop a dependence upon the antibiotics. These transformations were nonreversible heritable changes. By treating serial leukemic transfers with graduated doses of folic antagonist he demonstrated discrete stepwise increases in resistance. All these observations suggested that the changes were mutations.

The question remained, however, whether or not these changes were independent of the treatment. By adapting the "fluctuation test," utilized by Luria and Delbruck (1943) in studies on bacteria to his study of the leukemia cells, Law was able to demonstrate independence. Starting with a common source of leukemia cells, he established 15 independent sublines and carried each through six transfers. In the seventh transfer, cells of each independent subline but one were inoculated into 10 mice which were then treated with the antifolic compound. The remaining subline was in turn divided into 10 lines with 10 inoculated animals for each line and these were likewise treated. Variation in response of the independent sublines with significantly greater variation among the independent sublines than among the 10 lines formed by dividing the one subline, indicated that these changes had occurred prior to the treatment and were, thus, independent of the treatment. Hence, resistance could be considered as resulting from the selection of mutations occurring independently of the treatment. Basic information such as this is directly applicable to man.

SUMMARY

The following basic facts and concepts derived from studies of the genetics of cancer in mice are probably also applicable to cancer in man.

1. The occurrence of every type of cancer can probably be influenced to some degree by the genotype of the individual.

2. A common genetic basis for two or more types of cancer probably will not conclusively be shown unless common physiologic patterns preceding the occurrence of the different types of cancer can be demonstrated.

3. The expected type of inheritance in cancer is multiple factor inheritance

with alternative expression, the appearance of the cancer depending upon whether or not the combined effect of the genetic and non-genetic factors exceed certain thresholds.

4. Results suggesting dominance in cancer may be owing to fluctuation of the combined effects of genetic and non-genetic factors about physiologic thresholds.

5. Specific genes may influence the occurrence of tumors through various gene action paths. One gene may influence more than one type of tumor through the same or different paths, and one gene may exert the same or opposite effect upon the occurrence of different tumors.

6. Primary gene action may be localized in the cell that becomes malignant or it may become manifest through some general physiologic system such as the endocrine system or through its control of extrachromosomal agents such as the milk agent in mice.

7. Because of additive relationship of genetic and non-genetic factors, the effect of any exogeneous factor on the occurrence of cancer may depend upon the genotype of the individual. Conversely, the influence of the genotype upon the occurrence of cancer may depend upon the non-genetic factors acting upon the individual.

8. Studies on mutagenesis-carcinogenesis correlation and on dose response in the mouse have yielded information supporting the somatic mutation hypothesis. The carcinogenic response in mice of radiation and nitrogen mustard combined, however, does not support the hypothesis nor do certain correlation studies in Drosophila.

9. Resistance of neoplasms to therapy developed during treatment may have a genetic basis.

REFERENCES

ANDERVONT, H. B. 1941. Spontaneous tumors in a subline of strain C3H mice. *J. Nat. Cancer Inst.* 1: 737–744.

ANDERVONT, H. B. 1945. Fate of the C3H milk influence in mice of strains C and C57 black. *J. Nat. Cancer Inst.* 5: 383–390.

ANDERVONT, H. B., AND DUNN, T. B. 1950. Response of mammary-tumor-agent-free strain dba female mice to percutaneous application of methylcholanthrene. *J. Nat. Cancer Inst.* 10: 895–926.

ANDERVONT, H. B., AND STEWART, H. L. 1937. Adenomatous lesions in stomach of strain I mice. *Science*, 86: 566–567.

AUERBACH, C. 1949. Chemical mutagenesis. ***Biological Reviews*** **24: 355–391.**

BITTNER, J. J. 1936. Some possible effects of nursing on the mammary gland tumor incidence in mice. *Science* 84: 162.

BITTNER, J. J. 1945. Inciting influences in the etiology of mammary cancer in mice. *A.A.A.S. Research Conf. on Cancer* pp. 63–95.

BITTNER, J. J. 1952. Studies on the inherited susceptibility and inherited hormonal influence in the genesis of mammary cancer in mice. *Cancer Res.* 12: 594–601.

BITTNER, J. J., VISSCHER, M. B., BALL, Z. B., & SMITH, F. 1944. Mammary cancer and mammary structure in inbred stocks of mice and their hybrids. *Science*, 99: 83–85.

BOYLAND, E., & HORNING, E. S. 1949. Induction of tumors with nitrogen mustards. *Brit. J. Cancer* 3: 118–123.

BURDETTE, W. J. 1943. The influence of susceptibility to tumors induced in mice. II. Tumors induced by methylcholanthrene in the progeny of C3H and JK mice. *Cancer Res.* 3: 318–320.

BURDETTE, W. J. 1950. Comparison of mutation rate and tumor incidence in Drosophila treated with chemicals. (Abstract). *Records Genetics Society of America*, 19: 92–93.

BURDETTE, W. J., & STRONG, L. C. 1943. The inheritance of susceptibility to tumors induced in mice. I. Tumors induced by methylcholanthrene in five inbred strains of mice. *Cancer Res.* 3: 13–20.

CARR, J. G. 1948. Chemically induced mutations. *Brit. J. Cancer.* 2: 132–134.

CHARLES, D. R., & LUCE-CLAUSEN, E. M. 1942. The kinetics of papilloma formation in benzpyrene treated mice. *Cancer Res.* 2: 261–263.

COLE, R. K., & FURTH, J. 1941. Experimental studies on the genetics of spontaneous leukemia in mice. *Cancer Res.* 1: 957–965.

DERINGER, M. K. 1951. Spontaneous and induced tumors in haired and hairless strain HR mice. *J. Nat. Cancer Inst.* 12: 437–445.

DERINGER, M. K., HESTON, W. E., & ANDERVONT, H. B. 1945. Estrus in virgin strain C3H (high-tumor) and virgin strain A (low-tumor) mice and in the reciprocal (A×C3H) F_1 hybrids. *J. Nat. Cancer Inst.* 5: 403–405.

DUNN, T. B. Morphology of mammary tumors in mice. *In Physiopathology of Cancer.* F. Homburger, Editor. Paul B. Hoeber, Inc., New York, N. Y. In Press.

EDWARDS, J. E., HESTON, W. E., & DALTON, A. J. 1942. Induction of the carbon tetrachloride hepatoma in strain L mice. *J. Nat. Cancer Inst.* 3: 297–301.

GARDNER, W. U., & PAN, S. C. 1948. Malignant tumors of the uterus and vagina in untreated mice of the PM stock. *Cancer Res.* 8: 241–256.

GRADY, H. G., & STEWART, H. L. 1940. Histogenesis of induced pulmonary tumors in strain A mice. *Am. J. Path.* 16: 417–432.

GRIFFIN, A. C., BRANDT, E. L., & TATUM, E. L. 1950. Nitrogen mustards as cancer inducing agents. *J. Am. M. Ass.* 144: 571.

HESTON, W. E. 1940. Lung tumors and heredity I. The susceptibility of four inbred strains of mice and their hybrids to pulmonary tumors induced by subcutaneous injection. *J. Nat. Cancer Inst.* 1: 105–111.

HESTON, W. E. 1941. Relationship between susceptibility to induced pulmonary tumors and certain known genes in mice. *J. Nat. Cancer Inst.* 2: 127–132.

HESTON, W. E. 1942a. Genetic analysis of susceptibility to induced pulmonary tumors in mice. *J. Nat. Cancer Inst.* 3: 69–78.

HESTON, W. E. 1942b. Inheritance of susceptibility to spontaneous pulmonary tumors in mice. *J. Nat. Cancer Inst.* 3: 79–82.

HESTON, W. E. 1942c. Relationship between the lethal yellow (A^y) gene of the mouse and susceptibility to induced pulmonary tumors in the mouse. *J. Nat. Cancer Inst.* 3: 303–308.

HESTON, W. E. 1945. Genetics of mammary tumors in mice. A symposium on mammary tumors in mice. *A.A.A.S. Pub.* No. 22 pp. 55–84.

HESTON, W. E. 1946. Paths of gene action in mammary-tumor development in mice. *J. Nat. Cancer Inst.* 7: 79–85.

HESTON, W. E. 1949. Induction of pulmonary tumors in strain A mice with methyl bis (β-chloroethyl) amine hydrochloride. *J. Nat. Cancer Inst.* 10: 125–130.

HESTON, W. E. 1950. Carcinogenic action of the mustards. *J. Nat. Cancer Inst.* 11: 415–423.

HESTON, W. E., & ANDERVONT, H. B. 1944. Importance of genetic influence on the occurrence of mammary tumors in virgin female mice. *J. Nat. Cancer Inst.* 4: 403–407.

HESTON, W. E., & DERINGER, M. K. 1947. Relationship between the lethal yellow (A^y) gene of the mouse and susceptibility to spontaneous pulmonary tumors. *J. Nat. Cancer Inst.* 7: 463–465.

HESTON, W. E., & DERINGER, M. K. 1948. Relationship between the agouti gene and mammary tumor development in mice. *Acta. de L'union Internat. Contre le Cancer.* 6: 262–263.

HESTON, W. E., & DERINGER, M. K. 1949. Relationship between the hairless gene and susceptibility to induced pulmonary tumors in mice. *J. Nat. Cancer Inst.* 10: 119–124

HESTON, W. E., & DERINGER, M. K. 1951. Tumor development in backcross mice segregated in respect to the hairless and the pink-eye genes. *J. Nat. Cancer Inst.* 12: 361–367.

HESTON, W. E., & DERINGER, M. K. 1952. Test for a maternal influence in the development of mammary gland tumors in agent-free strain $C3H_b$ mice. *J. Nat. Cancer Inst.* 13: 167–175.

HESTON, W. E., DERINGER, M. K., & ANDERVONT, H. B. 1945. Gene-milk agent relationship in mammary-tumor development. *J. Nat. Cancer Inst.* 5: 289–307.

HESTON, W. E., DERINGER, M. K., DUNN, T. B., & LEVILLAIN, W. D. 1950. Factors in the development of spontaneous mammary gland tumors in agent-free strain $C3H_b$ mice. *J. Nat. Cancer Inst.* 10: 1139–1155.

HESTON, W. E., DERINGER, M. K., HUGHES, I. R., & CORNFIELD, J. 1952. Interrelation of specific genes, body weight and development of tumors in mice. *J. Nat. Cancer Inst.* 12: 1141–1157.

HESTON, W. E., & DUNN, T. B. 1951. Tumor development in susceptible strain A and resistant strain L lung transplants in LAF_1 hosts. *J. Nat. Cancer Inst.* 11: 1057–1071.

HESTON, W. E., & SCHNEIDERMAN, M. A. Analysis of dose-response in relation to mechanism of pulmonary tumor induction in mice. *Science,* In press.

HUSEBY, R. A., & BITTNER, J. J. 1948. Studies on the inherited hormonal influence. *Acta Union internat. contre cancer.* 6: 197–205.

KIRSCHBAUM, A. 1949. The induction of mammary cancer with methylcholanthrene; histological similarity between carcinogen induced tumors and certain mammary neoplasms occurring spontaneously. *Cancer Res.* 9: 93–95.

KORTEWEG, R. 1934. Proefondervindelijke onderzoekingen aangannde erfelijkheid von kanker. *Ned. tschr. geneesk.* 78: 240–245.

LARSEN, C. D., & HESTON, W. E. 1945. Effects of cystine and calorie restriction on the incidence of spontaneous pulmonary tumors in strain A mice. *J. Nat. Cancer Inst.* 6: 31–40.

LAW, L. W. 1948. Mouse genetics news. *J. Hered.* 39: 300–306.

LAW, L. W. 1951. Response of a resistant variant of leukemic cells to an antagonist of pteroylglutamic acid. *Proc. Soc. Exp. Biol.* 77: 340–344.

LAW, L. W. 1952a. Origin of resistance of leukemic cells to folic acid antagonists. *Nature.* 169: 628–629.

LAW, L. W. 1952b. The flexed-tail-anemia gene (*f*) and induced leukemia in mice. *J. Nat. Cancer Inst.* 12: 1119–1126.

LITTLE, C. C. 1934. The relation of coat color to the spontaneous incidence of mammary tumors in mice. *J. Exp. Med.* 59: 229–250.

LITTLE, C. C. 1941. The genetics of spontaneous tumor formation. *In Biology of the laboratory mouse.* Ch. 6. Blakiston.

LITTLE, C. C., MURRAY, W. S., & CLOUDMAN, A. M. 1939. The genetics of nonepithelial tumor formation in mice. *Am. J. Cancer*, 36: 431–450.

LORENZ, E., HESTON, W. E., DERINGER, M. K., & ESCHENBRENNER, A. 1946. Increase in incidence of lung tumors in strain A mice following long-continued irradiation with gamma rays. *J. Nat. Cancer Inst.*, 6: 349–353.

LURIA, S. E., & DELBRUCK, M. 1943. Mutations of bacteria from virus sensitivity to virus resistance. *Genetics.* 28: 491–511.

MACARTHUR, J. W. 1949. Selection for small and large body size in the house mouse. *Genetics.* 34: 194–209.

MACDOWELL, E. C., POTTER, J. S., & TAYLOR, M. J. 1945. Mouse leukemia XII. The role of genes in spontaneous cases. *Cancer Research* 5: 65–83.

MACKLIN, M. T. 1952. Genetical study of human mammary cancer. *Proc. Second Nat. Cancer Conf. In press.*

MOSTOFI, F. K., & LARSEN, C. D. 1951. The histopathogenesis of pulmonary tumors induced in strain A mice by urethan. *J. Nat. Cancer Inst.* 11: 1187–1221.

NETTLESHIP, A., & HENSHAW, P. S. 1943. Induction of lung tumors in mice with ethyl carbomate (urethane). *J. Nat. Cancer Inst.* 4: 309–319.

PYBUS, F. C., & MILLER, E. W. 1938. A sex difference in the incidence of bone tumors in mice. *Am. J. Cancer*, 34: 248–251.

SHAPIRO, J. R., & KIRSCHBAUM, A. 1951. Intrinsic tissue response to induction of pulmonary tumors. *Cancer Res.*, 11: 644–647.

SMITH, F. W. 1948. The relationship of the inherited hormonal influence to the production of adrenal cortical tumors by castration, *Cancer Res.* 8: 641–652.

Staff of Roscoe B. Jackson Memorial Laboratory, 1933. The existence of non-chromosomal influence in the incidence of mammary tumors in mice. *Science.* 78: 465–466.

STRONG, L. C. 1945. Genetic analysis of the induction of tumors by methylcholanthrene IX. Induced and spontaneous adrenocarcinomas of the stomach in mice. *J. Nat. Cancer Inst.* 5: 339–362.

STRONG, L. C. 1949. Induction of mutations by a carcinogen. *Proc. Eighth International Congress of Genetics. Hereditas.* Supp. vol. 486–499.

STRONG, L. C., & HOLLANDER, W. F. 1951. Spontaneous gastric neoplasia in mice of the Br-S strain incidence and genetic linkage tests. *Cancer Res.* 11: 94–99.

TANNENBAUM, A. 1940. Relationship of body weight to cancer incidence. *Arch. Path.* 30: 509–517.

VIDEBAEK, A. 1947. *Heredity in human leukemia.* Nyt Nordisk Forlag. Copenhagen. H. R. K. Lewis and Co. Ltd. London.

WAINWRIGHT, J. M. 1931. A comparison of conditions associated with breast cancer in Great Britain and America. *Am. J. Cancer.* 15: 2610–2645.

WOOLLEY, G. W., & LITTLE, C. C. 1945. The incidence of adrenal cortical carcinoma in gonadectomized female mice of the extreme dilution strain. I. Observations on the adrenal cortex. *Cancer Res.* 5: 193–202.

WRIGHT, S. 1934a. On the genetics of subnormal development of the head (otocephaly) in the guinea pig. *Genetics.* 19: 471–505.

WRIGHT, S. 1934b. The results of crosses between inbred strains of guinea pigs, differing in number of digits. *Genetics.* 19: 537–551.

A Panel Discussion[1]: Genetic Counseling

LEE R. DICE, Ph.D., Chairman

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INTRODUCTORY REMARKS OF THE CHAIRMAN

In this panel discussion on counseling in human heredity we shall take the down-to-earth approach of presenting actual cases and of asking persons who are experienced in giving counsel to state what advice they would give under the circumstances. The cases that are presented all happen to be concerned in considerable part with the probability that the children of a particular pair of parents will inherit defects known to occur in the family of one or of both parents or which have occurred in one or more of their children. This is one of the questions most frequently asked of the genetic counselor.

One point which I hope that the panel will consider in some detail is the kind of advice which the counselor should give. Should he restrict his advice to the probability that persons now alive or later to be born will exhibit certain defective traits which are known to occur in the family, or should he consider also future generations and the danger of harmful heredity persisting or accumulating in the population? Should he consider only the defective traits in question, or should he consider the whole heredity of the family, the valuable traits as well as the undesirable ones? And, finally, should he consider economic and social status, with, for example, the possibility that the support over many years of a seriously handicapped child might be a catastrophe for a family in modest circumstances, while it might be an unfortunate but endurable hardship for a wealthy family? In other words, just what factors should the genetic counselor consider in giving advice?

Case No. 1. Harelip and cleft palate

Young woman aged 27 years has had fairly successful surgery (5 operations) for harelip and cleft palate. Her parents (not related by blood), one younger brother, and all known ancestors have no trace of the defect. She is attractive but highstrung and emotionally tense; brilliant student working full time while studying for master's degree. Married to young man without any known serious defect, coming from normal family, and studying to become a teacher.

Statement by C. NASH HERNDON, M.D., Department of Medical Genetics, Bowman Gray School of Medicine, Winston-Salem, North Carolina:

In dealing with the problem presented by this young couple, it seems that

[1] Part of program of the fifth annual meeting of The American Society of Human Genetics, Ithaca, New York, September 7–10, 1952.

there are two major questions which require consideration. The first involves the genetics of harelip and cleft palate, requiring an estimate of the likelihood that the defect presented by the wife might reappear in the children of this couple. The second question is more complicated, involving some evaluation of the total genetic potential of this couple and their psychological status, these factors providing the general background against which the more specific question should be considered for proper overall evaluation.

In considering the specific defect, I believe that most authorities agree that we may distinguish two clinical varieties of cleft palate which are very probably distinct genetically. The variety seen less often is that of cleft palate which occurs alone, without association with harelip, this defect having a frequency of around 1 in 2,500 live births. The more common variety is presented by our patient today, this being the defect of harelip which may occur alone or in combination with cleft palate. This has a population incidence of about 1 in 1,000 live births. It is well recognized that incidence figures may vary considerably from one population group to another, and figures both higher and lower than those quoted have been reported for these defects in various special population groups. Figures in the general region of 1:1,000 for harelip with or without cleft palate and 1:2,500 for cleft palate alone have been reported for widely scattered population groups both in this country and in Europe.

Although much has been written concerning the inheritance of harelip and cleft palate, the genetic situation is still not entirely clear. The great majority of pedigrees that have been studied are rather irregular, and certainly the majority of patients seen clinically are similar to the one in our case for discussion, with only one affected individual in the family and no history of similar defect in any known relative. It is generally recognized that the incidence of harelip is not equal in the two sexes, with practically all authors reporting an excess of affected males usually in a ratio of nearly 2:1. To explain this sex difference, Fortuyn in 1935 suggested that two recessive genes might be involved, one autosomal and one sex-linked. In a careful analysis of the available data, Cotterman and Snyder showed that the assumption of a sex-linked recessive gene would not adequately account for the abnormal sex ratio observed. Further study of the general problem by Mather and his coworkers also demonstrated the inadequacy of the suggestion of a sex-linked recessive gene, and further suggest that possibly several different genes may be involved in different families, with one of these genes perhaps being partially sex-linked.

Animal studies have shed some light on the situation, several authors having reported on the situation in mice. The studies of Sheldon Reed suggest that the environment of the embryo may play a considerable part in expression of the gene or genes. It is entirely possible that a similar situation may exist in man.

Although the genetic situation in man is certainly not clear, the available evidence at present suggests that there are probably at least two and possibly

more genetically distinct varieties of harelip and/or cleft palate, apparently with autosomal inheritance with genes of reduced penetrance. The penetrance of the postulated genes is apparently twice as great in males as in females, and the penetrance may very well be influenced by the intrauterine environment of the individual.

As clear-cut predictions cannot be made from our present knowledge of the formal genetics of the disease, we must fall back upon empiric risk figures derived from observation of large numbers of similar cases. Such figures have been given by Jan Böök based on the experience of the clinics in Sweden, and seem to be in accord with the experience in our own clinic in North Carolina. Böök estimates the risk for children where one parent is affected by harelip with or without cleft palate and the other parent normal at 2%. This is less than the corresponding figure for cleft palate alone with one parent affected, which is quoted at 7%. Böök also gives figures for repetition of the defect within a sibship after one affected child has already appeared. For harelip with or without cleft palate, the likelihood that a second affected child may appear if both parents are normal is given as 4%, but if one parent is affected the likelihood of a second affected child is 14%.

For the family in question then, we would estimate the probability of recurrence of the mother's defect in her children at approximately 1 in 50 for each child. This is not an extremely high risk, but it is at least 20 times as great as the general population risk for this defect.

Turning to the second problem of the general background of this couple, our information is rather scanty but some tentative conclusions may be reached. From the statement made that the wife is a brilliant student studying for a master's degree and the husband also studying to become a teacher, one would assume that this couple is above average in general intellectual endowment. In the absence of information to the contrary, we may assume that they are otherwise physically normal individuals, the only reservation being the statement that the wife is highstrung and emotionally tense. One would wish for more information concerning the attitude of this couple toward children, as to whether they really want a family and are willing to provide a normal home and environment for possible children. Is the emotional tenseness of this young woman of sufficient degree to interfere with her role as a wife and mother in a normal family? It is of course possible that these young people do not want children to begin with, and are merely seizing upon the presence of an inherited defect in one of them as an excuse to rationalize their evasion of the responsibilities of parenthood. If further interviews with the couple should suggest that a situation of this type might exist, I would have no compunction in recommending that they remain childless, as they probably would not do a good job of raising children in any event.

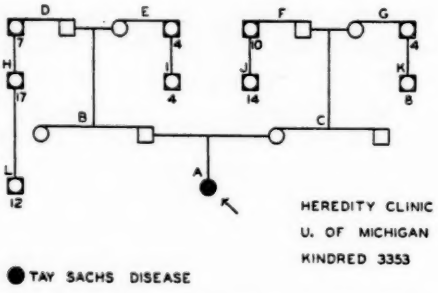
On the other hand, if further interviews should suggest that this couple really desire children and are emotionally prepared to accept them, I would further inquire concerning their probable emotional reaction in the event that the abnormality should appear in one of their children. Would the mother be able to accept this situation and adjust to it, or would it be an overpowering burden upon her conscience? Having had five corrective operations herself, the wife is in a position to perhaps understand what correction of this defect might mean more than the average individual. The technique of surgical correction of cleft palate defects has advanced considerably in the past 25 years, with operative mortality now being extremely low and with the percentage of functionally and cosmetically acceptable results being very high. The possible cost of surgical correction should not be considered an important deterring factor, even if the couple have very limited economic resources, as facilities for obtaining financial help with such repair operations are available in practically all states. In North Carolina, the Crippled Children's Division of the State Board of Health will authorize and finance operations of this type for any child from a family in economic difficulties due to this cause.

In conclusion, I would advise this couple that the likelihood that harelip or cleft palate might appear in their first child would be somewhere in the neighborhood of 1 chance in 50. It would seem that their intellectual endowments and general genetic background may be sufficiently above normal that their reproduction might be advantageous to society as a whole, offsetting the disadvantage of possible continuation of the defective gene. If the counselor feels that this couple could make a satisfactory psychological adjustment to the problems of normal parenthood, and further that they could adjust in a satisfactory manner if a defective child should appear, I would urge them to start their family fairly soon. As the wife is now 27 years of age, they have waited until fairly late in the normal reproductive period to begin a family, as is frequently the case in young persons taking professional training, and they should not delay much longer if children are really desired. There is some evidence that likelihood of appearance of the malformation in the children may increase somewhat with advancing maternal age, a phenomenon observed in many varieties of congenital malformation, and this should be borne in mind in urging them to reach a decision at a fairly early date.

I wish to emphasize that it is my feeling that the final decision should be made by the couple themselves. I feel that it is the responsibility of the counselor to present the facts and probabilities in the case to the couple as clearly and fairly as possible, and to advise them of all alternative possibilities. In the final analysis, the decision should be made by the couple themselves and the examiner should not try to urge them into a decision which they do not completely accept.

Case No. 2. Amaurotic idiocy—(Tay-Sachs disease)

The propositus is a first-born 9-months old girl with a diagnosis of amaurotic idiocy. The father is 31 years of age and the mother 27. Parents of above average mentality and well to do. In the extensive pedigree there is no evidence of consanguinity between the parents nor any other instance of amaurotic idiocy.



Statement by NORMA FORD WALKER, Ph.D., Hospital for Sick Children, Toronto, Canada:

In counselling these parents, I would not bluntly tell them that the chance of having another affected child is approximately 1 in 4. I would spend a good deal of time and gradually develop the argument which leads to the calculation of the probability. Since the parents in this particular case have "above average mentality" I would take time to try to explain to them that we are here dealing with a metabolic error, that the disease consists of a degeneration of the nerve cells apparently due to a biochemical deficiency that prevents the body from utilizing certain lipoid constituents of the brain cells. I would explain that this evidence is obtained histologically in the brain and liver. I would try to tell them about genes and their control of biochemical processes; also about the mutation of genes and finally why we believe that amaurotic idiocy is due to a single recessive mutant gene. From now on I would refer to the condition as Tay-Sachs disease, this term being much more acceptable to parents, lacking as it does the stigmata suggested by amaurotic idiocy.

I would point out that each parent is a carrier of this mutant gene and trace for them the method of inheritance, showing that for each child born to them there is 1 chance in 4 of his being affected. I would also make the point that although a child of theirs is unaffected, still he has 2 chances out of 3 of being a carrier.

I would enquire whether or not the parents are Jewish, since the ratio of Hebrew to Gentile parents is reported as 70:15.

The parents here described fit into the picture of a recent case which we had at the Hospital for Sick Children in Toronto. The parents were Jewish. The

father was a university graduate who had had some undergraduate work in genetics, the mother a college graduate whose family lives in New York. As is frequently the case, it was the mother who had made the early enquiries through her parents from pediatricians in New York (since she was blamed for the defective child). The father then enquired from pediatricians in Toronto. When the father came to see me as a geneticist, he presented me with a carefully prepared list of questions and I knew he was interested to see if my answers would tally with those they had received elsewhere.

Besides the genetical risk involved, he wished to know whether or not there was a common genetic basis for infantile amaurotic idiocy, juvenile amaurotic idiocy and adult forms. His point was: Might they have a child who would appear normal for some years and then develop the disease? He wished to discuss artificial insemination (1) if the donor were Jewish (2) if the donor were Gentile. Like very modern young parents they had tentatively made their plans to have a second child by a donor and then take a chance of having a third child of their own.

In answer to his question concerning a common genetic basis for infantile and juvenile forms of amaurotic idiocy, I assured him that the two types appear to be quite distinct. The juvenile form is also the result of a rare recessive factor, but it does not show the racial predilection which the infantile form does.

Concerning late amaurotic idiocy, the number of patients recorded is still too small to determine the exact genetic mechanism but there is no reason to suspect any association with the infantile form.

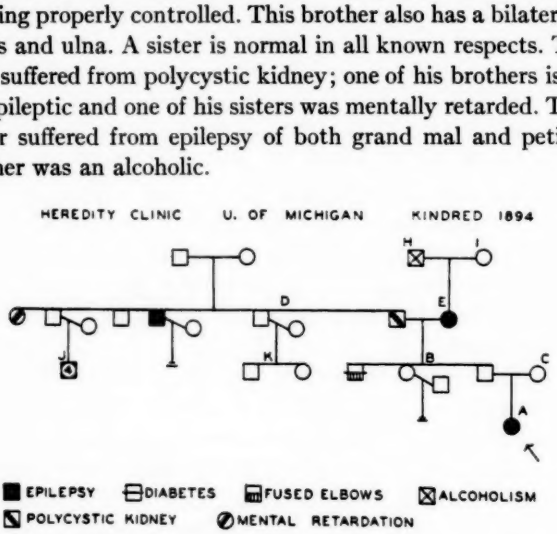
Concerning artificial insemination with a Jewish donor the probability that the donor would be a carrier would be something of the order of 1 in 100; with a Gentile donor the chance would be far smaller, perhaps of the order of 1 in 200. However with either donor there is half a chance that the child born will receive a mutant gene from the mother and so be a carrier. The undesirable gene is thus perpetuated, and a consanguineous marriage for such a child should be avoided.

In conclusion I may cite another case which we have in our hospital this summer and which presents a quite different picture. The parents were Gentiles, and came from an isolated part of Newfoundland. Although they knew of no consanguinity, it might well be suspected that it existed in that small isolated community. Economically they were a poor family, living in rooms. They had two normal and two affected children and the care of the affected children was a very great burden. The mother in this case was very glad to have the genetics of the defect explained to her and to be encouraged to limit her family.

Case No. 3. Epilepsy and other abnormalities

Propositus is a female child aged 2 years, who has had convulsive seizures since the age of 6 months. Father aged 25 years is of a well-to-do family. Has

master's degree from a large university and exhibits no abnormalities; his pyelograms are normal. Mother is unrelated by blood to father and is a nurse, but little is known about her family. An elder brother of the father has diabetes and has had several convulsions, which are believed to be due to insulin treatment not being properly controlled. This brother also has a bilateral synostosis of the radius and ulna. A sister is normal in all known respects. The paternal grandfather suffered from polycystic kidney; one of his brothers is reported to have been epileptic and one of his sisters was mentally retarded. The maternal grandmother suffered from epilepsy of both grand mal and petit mal types and her father was an alcoholic.



Statement by SHELDON C. REED, Ph.D., Dight Institute, University of Minnesota, Minneapolis, Minnesota.

In the present case of a two-year-old girl with convulsive seizures, some of the background information is lacking which is necessary for the complete answer. It is obvious, from the statement given, that there were convulsive seizures on both sides of the family of the father in which the little girl was born. It becomes necessary to assume that her seizures have a genetic basis, and to so instruct the parents. The chance that each sibling of this child will also have seizures seems to be roughly between two and five per cent. Yesterday, Dr. Metrakos showed that for her still rather small sample, the incidence in the sibs was as high as 19%. Consequently, if the couple have subsequent children, there is a real chance that one or more of them will also have seizures.

The information which is most needed, but lacking, is that of the attitude of the parents toward this child and an estimate of what their attitude toward a possible subsequent child with seizures might be. It is not practical to expect that extensive psychoanalysis will be possible in genetic counseling cases, but the general reactions of both parents to the situation can be obtained. Better acquaintance with the parents may be obtained by asking them to obtain electroencephalographs for themselves. After these have been obtained and read by an

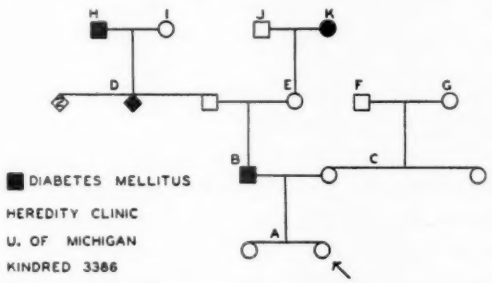
expert, you can get to see the parents again to inform them of the impressions obtained from the EEG's. Without a reasonable acquaintanceship with the parents, it would be impossible to advise them whether or not to have more children. I would "soft-pedal" the problem of the possibility of the inheritance of the polycystic disease as the father's x-ray was negative. The seizure problem is enough.

It appears, from the information given, that medication for the little girl has not been very successful. Apparently, she will have to be institutionalized or suffer the severe social discrimination which will be her lot if she attends ordinary schools. Provision for the future of this child is a serious problem and affects, materially, the decision of the parents regarding future children.

If the genetic counselor is to advise the couple as to whether they should have more children or not, he must consider all the psychological, social, and economic factors he can find out about. It is an extremely rare case, which, in the experience of the Dight Institute, can be advised outright, as to whether or not reproduction is indicated. The counselor has never suffered the particular circumstances which the parents of the affected child suffered and therefore cannot completely understand their feelings.

Case No. 4. Diabetes

Propositus is a white female aged 2 years, weighed 8½ lbs. at birth, in good health. Well-to-do father is diabetic and reports that a sib of his father of unknown sex, his paternal grandfather, and his maternal grandmother all suffered from diabetes. Mother of propositus not diabetic and no record of diabetes in her family. She is unrelated by blood to the father.



Statement by C. P. OLIVER, Ph.D., Department of Zoology, University of Texas, Austin, Texas.

One who is asked by a person to discuss a family history frequently find that he can not get all of the data he wants to prepare answers to the questions. Yet the problem may be pressing enough to the family that the adviser feels it necessary to do the best he can with the information available.

In this family, we know that a young girl is diabetic. Her father is diabetic. We have no data on the age of onset, severity or therapy relative to this father. It is reported that his paternal grandfather and maternal grandmother and one other relative, a sib of his father, were diabetic. This information can not be fully accurate because the man does not know the sex of that sib. The grandparents might have been glycosuric but not diabetic. Actually the man's father or mother might have been a potential diabetic.

Good advice can nevertheless be given to the father and mother of the diabetic daughter regardless of the accuracy of the data in the older generations. The fact that a history of diabetes in the family is reported will make the parents accept a genetic interpretation more readily. I am assuming, of course, that the diagnoses in the last two generations are accurate.

One can and should tell the parents that many if not most cases of diabetes have a hereditary basis. This conclusion is supported by family histories in which diabetes occurred in several members of a family in more than one generation, as in the family under discussion. Evidence in favor of heredity is found also in twin studies in which one or both members are affected. Monozygous twins have both members affected with a higher relative frequency than do fraternal twins. Not all of the reported cases on monozygous twins show this concordance. Therefore it is probable that all cases are not due to a hereditary tendency. This will be referred to later in discussions of latent cases.

The mechanism of inheritance would be discussed only if the parents asked about it. Here we encounter the first major complication. Investigators do not agree as to the mechanism. Considering those theories of one gene or one gene-pair being effective in diabetes, we find different interpretations. Some report a dominant Mendelian inheritance in certain families, and that is probably a correct interpretation. A few believe that a dominant gene of low penetrance is responsible. One report gives evidence of sex-linkage. Many workers have concluded that diabetes is a result of a pair of recessive genes on the autosomes. (Mendelian recessive.)

In the family in question, the mechanism of inheritance will have little effect on the answer as to the probability that their children will be affected. The father is diabetic. For the first discussion we can assume that the mother is phenotypically normal for the trait. If the trait is dominantly inherited, although the father's parents are reported to be normal, each child has a 1 to 1 chance of receiving the dominent gene from him. The odds are against his being homozygous for the dominant gene.

If the trait is recessively inherited, as it could be in this history, the father will transmit a gene for the potentiality to each child. We began with a working assumption that the woman is normal for the trait. She could be told that under the theory of recessive inheritance, we would conclude that she is hetero-

zygous. This is evidenced by her first child who is diabetic. It sometimes helps if you can show that both families are responsible. Therefore whether a child has the homozygous genotype for diabetes or is heterozygous but not diabetic will depend upon the gene inherited from the mother. This will also be a 1 to 1 chance. The same reasoning will apply if the trait is sex-linked.

It is possible, therefore, to give an answer to the parents as to the probable inheritance of the genotype which will condition a potential diabetic child. He will have an equal chance of having or not having that potentiality.

In all fairness, and to prevent misunderstandings, one should state the risk that other children face on the basis of data which have been worked out. The next child will not have a 1 to 1 chance of becoming diabetic during the expected life of the parents. In families having a diabetic parent and one affected child, about 1 in 9 of the other children have been reported also to have the disease, at least if we consider only the earlier years of life. However, some of these "normal" sibs will be potential diabetics and may later in life develop the disease. If they are not recognized as diabetics some can be expected to transmit the gene to their children. There are more undiagnosed than diagnosed cases of diabetes. The early age of onset in the first child will not affect the frequency of diabetes in her sibs. This we can say even though there seems to be a positive correlation in the ages of onset of siblings.

We have been asked to show how far we would go in giving advice about having other children. I believe that we should look to the future but we should use discretion in how we emphasize this to parents. We should outline the possible conditions to the parents. They must decide whether they will have more children. However, I believe it is unfair to a child to start him out in life with a handicap to compete in our society. Consequently it seems wise to do more than just give the probability that the good or bad will occur. We should let the parents know the worst part of the picture. Therefore I would go farther in my discussions.

In the case at hand, one might refer to the mother's condition, whether she is a potential diabetic. Her first child weighed 8½ pounds at birth. This is above average but is within the normal range of weight of the newborn. We do not know what factors might be given as explanations for the large-size baby. Nevertheless the mother should be asked whether she has been tested for glucose tolerance. If she is a latent diabetic of the recessive type similar to that of her husband, every child will be a potential diabetic—with early or late age of onset. If the mother is not diabetic, we should emphasize that all children normal in phenotype will need regular examinations throughout life. They will never feel secure in having continued good health. When a child becomes old enough to take care of himself the worry and anguish will pass from the parents to himself. Persons homozygous for the gene may remain free of symp-

toms for many years. The fact that the first child and possibly the father had an early onset does not necessarily mean that all other diabetic sibs will have an early onset. Severity is not the same in all affected sibs. If he has a later age of onset it may occur at the time his own family most needs his support. In genetics we also know that conditions of life can change dominance of a gene so that a heterozygote may show the disease ordinarily behaving as a recessive. Therefore the carriers face a risk.

Geneticists do in one way or another think about accumulation of good and bad genes in the population. Not many parents, though, are ready for that type of discussion. It is therefore necessary again to get over the idea without actually making the statement.

Suppose this family has traits which are considered desirable. We need to decide, then whether the good outweighs the diabetes, which we will call the bad. We will even assume that the good traits have a hereditary basis and that the relative effects of heredity and environment are known.

Society might decree that we need and should preserve these good traits. If the parents have other children, some of them will probably escape diabetes and may have the desirable traits. If a child has both diabetes and the good trait, genetic recombinations (independent assortment) will separate the two in the next generation. Some would say that the parents should therefore continue child bearing.

This is an extreme opinion, quite opposite from the one against child bearing. It is one which would keep the bad to preserve the good. It is reasoning against the individual. One might say that therapeutic means are available to preserve life of the diabetic and to make life bearable. We can *not* say that the person will be assured that he can lead a normal life, certainly not if the disease is severe enough to require insulin.

Possibly one might conclude that the child in the family has a 1 to 1 chance of not having diabetes anyhow. He would be at the best heterozygous. Some persons might be willing to take this gamble. We must show, though, that the gamble is taken at the risk of the child. He will face the need to live with the extra hazard if he becomes diabetic. If he is normal, the child is heterozygous and therefore must decide about his own progeny. We should weigh our discussions with the parents in favor of the child.

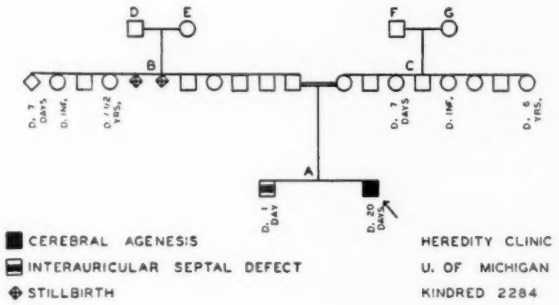
In our case the father is well-to-do. He can take care of the girl and possibly other diabetic children. Again, though, the thought should not be altogether on the costs or lack of expense to society in charity. The child deserves some consideration. Wealth has a way of slipping out of hands—more than by taxes. If the girl marries, or if a potential diabetic marries, the husband may not be as well-to-do as the father. She may marry a school teacher—too proud to live off the parents-in-law, too poor to meet more than the bare necessities of

life. The child then suffers regrets because the father did not think about the difficulties that his child might face.

I stated that the parents should make their own decision after they have all the facts available. Therefore I would not tell the father those last mentioned opinions. But I would make the picture as dark as possible to help him reach that conclusion.

Case No. 5. Serious abnormalities in two children

Father, well-to-do, age 27, and mother, age 19, related both as second cousins and as second cousins once removed. First child, a male, weighing 1600 grams and born by Caesarian operation, died on day of birth. An autopsy showed an interauricular septal defect and markedly hypoplastic adrenals. Second child, a male, also born by Caesarian, had decerebrate rigidity, failed to suck adequately, twitched constantly, and died after a few days. Cerebral agenesis was noted at autopsy. The first infant in the sibship of the father died at about 7 days of age, believed caused by an infection, possibly tetanus, following a midwife-assisted delivery in Iraq; a sister died in infancy and another sister at age of 1½ years of unknown causes; 2 successive stillborn infants were premature; a sister and 4 brothers are reported alive and well. Of the mother's sibship, 2 sisters born in Iraq are reported each to have died within a few days of birth with symptoms similar to those of her first-born defective child described above. Another sister is reported to have contracted typhoid fever, after which she developed a partial paralysis and was unable to talk; she died at the age of 6 years. Three brothers and one sister of the mother are reported normal.



Statement by JAMES V. NEEL, M.D., Ph.D., Heredity Clinic, University of Michigan, Ann Arbor, Michigan:

The significance of the history of neonatal mortality in the parental sibships in this pedigree, and the significance of the consanguinity between the parents

in relation to the observed defects in their children, are difficult to evaluate because of our relative ignorance of what the normal base line is for Iraq. If we disregard these facts, we are left with two neonatal deaths. Autopsy in the first child revealed an intra-auricular septal defect, the significance of which in a child weighing only 1600 grams is uncertain. Autopsy in the second child revealed cerebral agenesis. We saw no particular evidence of a genetic cause of death in the first child, although of course that possibility could not be excluded, but felt that the cerebral agenesis of the second might well be due to a recessive gene. Balancing the various probabilities together as best we could, we informed the parents that the chance that they might lose subsequent children in a similar fashion was probably in the neighborhood of 1 in 4.

If the chair will permit me, I should like to proceed from the discussion of this case to some general remarks about the problem of genetic counselling. We at Michigan find that almost invariably after the probabilities involved in a particular situation have been explained to a couple, the question follows: "Doctor, should I have any children?" or "Doctor, should I have more children?" While we attempt to leave that decision to the individuals in question after they have been acquainted with all the facts at our disposal, it is difficult to avoid influencing the decision one way or the other. I, for one, must confess that each year, as my experience broadens, I am finding it more difficult in my own mind to answer some of these questions concerning the advisability of reproduction. The reasons for this are chiefly two. To begin with, while there are certain black-and-white situations in which we would all agree as to the desirable course of action, there are many more where the issue is much less clear cut. As our knowledge of man's genetic constitution increases, we realize that most of us are heterozygous for some one or several undesirable genes—those who consult us at the Clinic are often only those who have had the misfortune to make a marriage that exposes in part the unfavorable side of their genetic constitutions. We really know precious little about human inheritance, nor do we know much more about our genetic needs 100 years hence. Genetic processes move slowly. I am reluctant on the basis of fifty years of knowledge to try influencing the evolution of an organism which has been a million years in the making.

My second cause for mental reservations in the field of genetic counselling is this: When a couple consults us with a genetic problem, it usually involves only a very few of the 20,000 or so genes each of us possesses. The temptation is strong to concentrate only on that aspect of the genome which brings the couple to us. But is that proper or wise? To take a specific example—amaurotic idiocy. Parents who have produced such a child have a 1 in 4 chance of a repeat in any subsequent pregnancy. Yet we have several times been consulted by otherwise genetically and sociologically superior families in which this situation

has occurred where I have said in effect: If you are prepared to risk the emotional trauma of another such child, then by all means, try again. You have far more than the average to offer the normal child you will probably have.

The science of human genetics has several times been in difficulty because an involved situation has been attacked with more audacity than perspicacity. It would be most unfortunate if in the present interest in genetic counseling this happened again. It would be particularly unfortunate at the present time, when we find ourselves at the apex of an ideological battle, and under the kind of scrutiny where a few mistakes go a long way.

CONCLUDING REMARKS BY THE CHAIRMAN

In summarizing the results of this conference it is evident that the counsel on heredity which is given to families must be based on what we know about the inheritance of human traits. Some human characters can be clearly identified and their mode of heredity can then be ascertained. We can estimate with some confidence the probability that a future child will exhibit such a trait, be it a defect or a superior character. For many human traits, unfortunately, we do not know the precise mode of heredity. We cannot, therefore, predict precisely what the probabilities are for the reappearance of such a trait among the children. For these traits our predictions must be based in considerable part on the frequency of their occurrence in the general population. Evidence about heredity given by the occurrence of the trait in the pedigree of the particular family concerned also is very useful.

More information than we now possess about the heredity of all types of human traits would obviously be extremely useful to the genetic counselor. This is particularly true of mental traits. We know much more about the heredity of severe physical abnormalities than we do about the heredity of mental differences. We know only a little about the heredity of superior health and superior mental characters. Much more research in the general field of human heredity, therefore, is needed in order to secure a firm basis for advice.

I am particularly pleased by the stress which the panel has given to the necessity for considering factors other than heredity in giving genetic advice. The panel is agreed that we must take into consideration the economic and social situation, as well as the general hereditary value or character of the family or of the individual concerned. Even the attitudes of the parents toward children are an important consideration. We must also, as Dr. Oliver has urged, keep the welfare of the child in mind.

This brings up, then, the problem of the education of genetic counselors. If we are going to take into consideration the social position and the economic position of the individuals concerned, our genetic counselors should know more than just genetics. They need. and should have, some training in social science. I

am not just sure what particular courses they should take, but they certainly should have a very broad training.

Furthermore, the panel stressed, and I think very wisely, the consideration of the heredity of future generations. We must give due concern to the possibility of eliminating or, perhaps, of perpetuating, undesirable or desirable genes. We must not only be concerned with the particular family concerned, but also with whether or not harmful heredity may be continued or expanded in our population.

Panel Discussion: Nomenclature in Human Genetics

C. P. OLIVER, Chairman

Department of Zoology, University of Texas, Austin, Texas

CHAIRMAN'S REPORT

A few years ago committees of workers in the United States and from other countries made a joint study on nomenclature in human genetics. The survey brought to our attention the complications and difficulties associated with the problem. Since that time, progress in human genetics has been rapid. The tendency towards chaos because of absolute individualism in naming traits and using symbols has become more marked. As a consequence, a symposium on nomenclature was held at the annual meeting of the Society. Members of the panel were R. C. Cook, H. B. Glass, F. B. Hutt, M. T. Macklin, P. Levine, C. Stern, H. H. Strandskov, A. S. Wiener, and C. P. Oliver. The audience also participated in the discussions.

The participants traded opinions in a general discussion of some of the problems in nomenclature. No attempt was made to agree upon definite rules. The meeting was organized in an attempt to determine whether members of the Society think that rules on nomenclature are desirable and whether such rules might aid in the study and reporting of human genetics.

Members of the Society attending the symposium agreed that the President of the Society should appoint a Committee on Nomenclature. This Committee would cooperate with an international group. There was general agreement that the problems on nomenclature should be considered at the International Genetics Congress in 1953.

In the meantime the committee of the Society can help our members by recommending orderly procedures to be followed. The panel made certain suggestions but did not have time to consider all of the problems. Some of the points discussed by the panel members and the audience are referred to in this report.

Synonyms are undesirable. Yet investigators reporting in human genetics are likely to add to the list already too large. A geneticist may find it difficult to identify certain traits properly. He may solve his problem by cooperating with an individual who is competent to identify the trait but this procedure will meet only part of his needs. The Society might do well to consider making available to human geneticists a list of "names" of traits, including synonyms. Lists now prepared and in print will be useful in the preparation of the article.

Investigators differ in their use of terms to describe the mechanisms of inheritance of genes on the sex-chromosomes. Some speak of sex-linkage for genes on the non-homologous region of the X-chromosome, Y-linkage or allosome inheritance for genes on the non-homologus area of the Y-chromosome, and partial or incomplete sex-linkage for genes on the homologous regions of the X- and Y-chromosomes. Others prefer the terms X-linkage, Y-linkage, and X-Y-linkage, respectively. Regarding these questions there was no unanimity of opinion to be derived from the discussions in the symposium.

The use of symbols to represent genes became a subject of considerable discussion evidencing lack of common practice. This is true whether one considers a locus with only two known alleles or one with multiple alleles.

One group prefers to follow the method of using a letter as a symbol if only one pair of alleles for a locus is known. The capital letter would indicate the dominant allele; the small case letter, the recessive. Under certain circumstances two or three letters might be necessary, but only the first one would be capitalized to represent the dominant allele. As other alleles become known, changes could be made to fit the new conditions.

Another opinion expressed was that a base letter be used as a symbol for the locus with superscripts to indicate the pair of alleles. The locus-symbol would identify the general function of a locus, or possibly the system involved. Superscripts would serve to indicate the product or particular effect of an allele. It was suggested that this method of using symbols would simplify discussions of gene action. Superscripts could show the dominance of one allele or lack of dominance. As new alleles are discovered, additions to the superscripts could be made.

Duplicate usage of one symbol to represent more than one locus is becoming a problem. Symbols should nevertheless be suggestive of the trait referred to. One method to avoid duplication is to use more than one letter for a symbol if the first letter has been used by someone else. This brings up the question of priority which can be settled only by a clearing center. A list of symbols accepted because of usage in the past can be used to prevent duplication.

Rules on the use of symbols should be kept as simple as possible so that additions to alleles can be made with a minimum of change in the symbols. The rules should be flexible enough that they can be abandoned or modified if additional data make changes necessary. Ease of printing should be considered. Publishers find it difficult to print both superscripts and subscripts and one should be discontinued. There is a preference for the use of superscripts to show multiple alleles. A number of geneticists dislike the use of primes as well as other symbols which may be misunderstood.

Symbols should represent the genetic facts as clearly as possible. Priority ought to be recognized. If the symbols now in use are inadequate, changes

should be made in accordance with good usage of genetic symbols unless such changes might result in harm. Where differences of opinion exist as to which list of symbols is correct, recommendations by a committee should be based upon the desire to cause least complications for professional men who use the symbols in their practice. Differences in opinion arise from difficulties in interpreting genetic data and because of the various genetic interests of the workers. Any existing inequalities should be straightened out by agreement.

A Genetic Study in Hereditary Spherocytosis[1]

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HEREDITARY SPHEROCYTOSIS (congenital hemolytic icterus; familial acholuric jaundice) is generally recognized as a Mendelian dominant blood disorder characterized clinically by anemia, jaundice and enlargement of the spleen. The single most important laboratory finding is the presence of microspherocytic red blood cells. The mean cell diameter is consistently smaller than in the normal person and averages 6.4 microns. The normal mean red cell diameter is approximately 7.4 microns. Other significant laboratory tests reveal reticulocytosis and increased red cell fragility to hypotonic saline solutions.

The determination of the presence of the disease in blood relations is important in confirming the diagnosis in the patient under observation. The clinical manifestations of the disease vary widely from time to time in affected members of the same family. It is essential that a correct diagnosis be established because removal of the spleen will result in permanent relief of anemia and jaundice. Conversely, in the acquired types of spherocytic hemolytic anemia, splenectomy often fails to be of value.

Laboratory studies have shown that the microspherocytes have an average life span of 15 to 30 days in the presence of the spleen. After splenectomy the microspherocytic cell has a normal life span of 90 to 120 days. In hereditary spherocytosis the characteristic small red blood cells persist after splenectomy and the disease is transmitted to the offspring in the usual manner after surgical intervention.

A farmer, age 65, was examined at the Cleveland Clinic and found to have a mild chronic type of hereditary spherocytosis. Because the family history suggested the presence of many affected relatives, this hereditary study was undertaken.

In April 1951, 154 members of 56 related families were personally interviewed in their homes in the Ohio-West Virginia area (Fig. 1). The majority of the families lived in a small valley in West Virginia. Blood smears of the 154 related persons and 26 of their mates were studied in the hematology section of the Cleveland Clinic. The mean red cell diameter was determined by the Haden erythrocytometer in addition to direct study of the Wright-stained smears. Only 9 of the 56 families revealed evidence of the disease. Of the 38

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[1] We wish to thank Dr. A. H. Hersh, Professor of Biology, Western Reserve University, for his counsel and guidance in this report.

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members under consideration in these 9 families, 16 had hereditary spherocytosis. Two others, dead at the time of this investigation, were proved to have had the disease by a review of their hospital records. Three other deceased

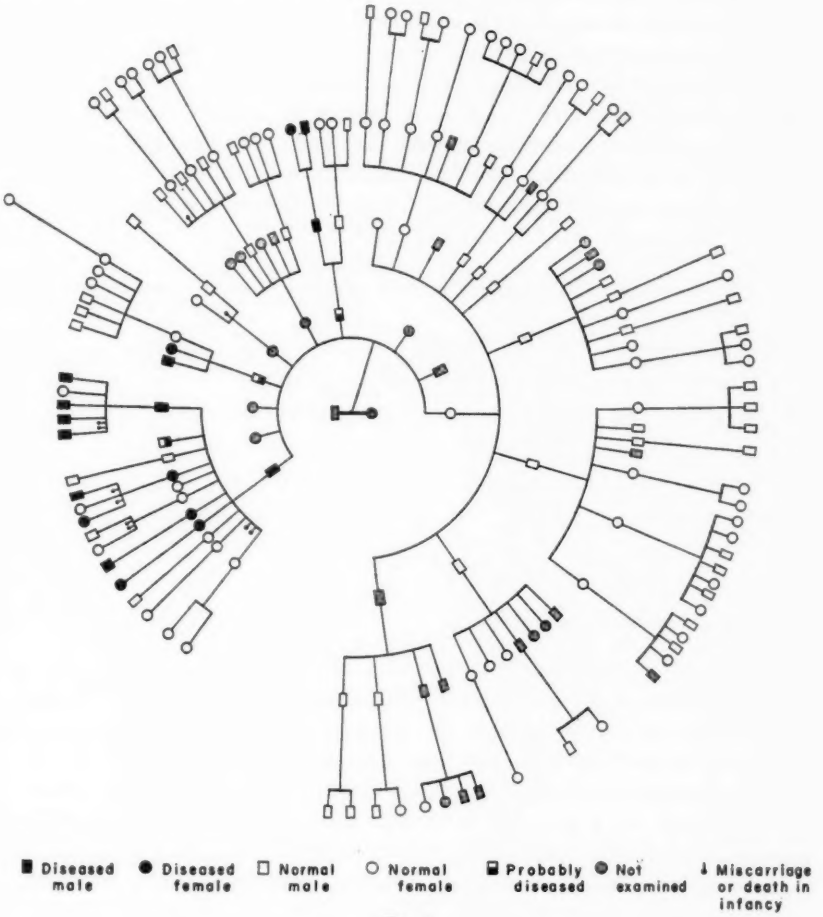

FIG. 1

persons, who had no hospital records, were listed as probably afflicted on the testimony of their relatives who said they had suffered "yellow spells".

The presence of a fully penetrant dominant allele is immediately detected by the presence of its corresponding phenotype. When the dominant allele is rare, as it is in this disease, the phenotype, in all probability, is due to a heterozygous condition *Dd* (where *D* is the dominant gene and *d* is its normal reces-

sive allele). Marriages between affected individuals (*Dd*) and normal individuals (*dd*) (as shown by this pedigree in all 9 cases) should theoretically result in a 1:1 ratio of the dominant to the recessive phenotypes of their progeny. In applying this a priori expectation to hereditary spherocytosis the "standard error" test for goodness of fit was used. Hogben (3) has shown the necessity of correcting for small family size. As shown in table 1, the observed number of affected persons is 21, and the expected number is 21.185, a difference of 0.185. The standard error, which is the square root of the total variance, is ±2.78. There is no significant difference between the number observed and the number of expected after correction, which indicates that a 1:1 ratio is a good fit. The data, therefore, support the conclusion that the disease is a simple dominant with full penetrance.

TABLE 1. CORRECTION FOR SMALL FAMILY SIZE WHERE $p = \frac{1}{2} = q$ (from Hogben)

SIZE OF FAMILY (S)	NUMBER OF FAMILIES (N)	CORRECTIVE FACTOR $\frac{Sp}{1-q^s}$,	JAUNDICED		VARIANCE FOR ONE FAMILY	TOTAL VARIANCE
			Expected (N) $\frac{(Sp)}{(1-q^s)}$	Observed		
1	2	1.000	2.000	2	0.000	0.000
2	2	1.333	2.666	3	0.222	0.444
3	2	1.715	3.430	4	0.489	0.979
5	1	2.581	2.581	4	1.082	1.082
10	1	5.005	5.005	3	2.478	2.478
11	1	5.503	5.503	5	2.737	2.737
Total.....	9		21.185	21		7.720

An attempt was made to determine the frequency of hereditary spherocytosis in the general population, but no reliable data are available. There appears to be a higher frequency of the disease in men than in women. In table 2a the "chi square" method is used for measuring the "goodness of fit". *P* is found to be between 0.1 and 0.2. When these data are pooled with those of Race (4) (table 2b) *P* is found to be 0.05. That the frequency of the disease appears to be higher in men is also confirmed by the fact that, of the total 38 members of the 9 families under consideration, there are 17 males, 14 of whom are diseased. There are 21 females, of whom only 7 are diseased. Because of the small sample, however, more data are needed to determine conclusively the exact percentage by which the incidence is greater in men than in women.

Race (4) in his report indicated that spherocytosis is "one link in the chain of general hereditary degeneration." In this study, therefore, hair and eye color, color blindness (red-green), handedness, midphalangeal hair, premature graying, miscarriages, taste blindness, gallstones and leg ulcers, were checked and tabulated. The only case of leg ulcers recorded was found in a diseased woman.

Four cases of gallstones were found, 2 occurring in affected persons and 2 in normal individuals. However, all 4 cases occurred within members of the 9

TABLE 2a. SEX DISTRIBUTION

	AFFECTED MALES	AFFECTED FEMALES
Observed	14	7
Expected (e)	10.5	10.5
Difference (d)	3.5	3.5
d^2/e	1.17	1.17

$X^2 = 2.34$. $N' = 1$. P is between 0.1 and 0.2

TABLE 2b. DATA OF RACE ON SEX DISTRIBUTION POOLED WITH PRESENT

	AFFECTED MALES	AFFECTED FEMALES
Observed	51	33
Expected (e)	42	42
Difference (d)	9	9
d^2/e	1.93	1.93

$X^2 = 3.86$. $N' = 1$. $P = 0.05$

TABLE 3. TASTE TEST RESULTS

	a. IN ENTIRE PEDIGREE	b. IN 9 AFFECTED FAMILIES			c. IN NON-RELATED MATES
		Affected	Non-Affected	Total	
Taster	59	1	1	2	12
Nontaster	53	9	6	15	11
Total	112	10	7	17	23

TABLE 4. EYE COLOR

	AFFECTED	NORMAL	TOTAL
Blue	8	4	12
Brown	7	6	13
Total	15	10	25

affected families. The results of the taste blindness tests (phenylthiocarbamide) were inconclusive as indicated in table 3a, b and c. In table 3a we are investigating 112 blood relatives and, therefore, it is not exceptional that a 1:1

TABLE 5. RESULTS OF INTERVIEWS WITH 9 DISEASED FAMILIES

Pedigree Number	Age	Sex	Eye Color	Color-blind Test	Hair Color	Handed	Mid-phalangeal Hair	Premature Gray Hair	Gallstones	Leg Ulcer	Miscarriage	Taste Test	Diseased	
													Proven by Blood Smear Study	Probable
I-1	43*	M												+
II-1	37*	M											+	
II-2	29*	F											+	
II-3	46	F	Br.	—	Br.	Rt.	—	—	—	—	—	+	—	
I-2	80*	M												+
II-4	45	M	Br.	—	Br.	Rt.	+	—	—	—		—	—	
II-5	47	M	Br.	—	Br.	Rt.	+	—	+	—		—	+	
III-1	18	M	Br.	—	Br.	Rt.	+	—	—	—		—	+	
III-2	25	F											+	
I-3	65	M	Bl.	—	Black	Rt.	+	—	—	—		—	+	
II-6	42	M	Bl.	—	Red	Rt.	—	—	—	—		—	+	
III-3	15	M	Br.	—	Br.	Rt.	—	—	—	—		—	+	
III-4	10	F	Br.	—	Br.	Rt.	—	—	—	—		—	—	
III-5	12	M	Br.	—	Br.	Rt.	—	—	—	—		—	+	
III-6	8	M	Br.	—	Br.	Rt.	—	—	—	—			+	
III-7	7	M	Br.	—	Br.	Rt.	—	—	—	—		—	+	
II-7	31*	M												+
II-8	28	M	Br.	—	Br.	Rt.	+	—	—	—		—	—	
II-9	40	F	Bl.	—	Red	Rt.	—	—	+	+	2		+	
III-8	13	M	Bl.	—	Br.	Rt.	—	—	—	—		+	+	
III-9	10	F	Bl.	—	Br.	Rt.	—	—	—	—			—	
III-10	0.5	F	Bl.		Blond		—	—	—	—			+	
II-10	39	F	Br.	—	Red	Rt.	—	—	+	—	—		—	
II-11	36	F	Bl.	—	Red	Rt.	—	—	+	—	2		—	
II-12	33	F	Bl.	—	Blond	Rt.	—	—	—	—	—	—	+	
III-11	11	M	Bl.	—	Blond	Rt.	—	—	—	—		—	+	
II-13	32	F	Bl.	—	Blond	Rt.	—	—		—	—		+	
III-12	3	F	Br.		Blond	Rt.	—	—	—	—			+	
II-14	21*	F											—	
II-15	23	F	Bl.	—	Blond	Rt.	—	—	—	—	—	—	—	
II-16	20	F	Bl.	—	Red	Rt.	—	—	—	—	—	—	—	
I-4	82	F	Br.	—	Black	Rt.	—	+	—	—	—	—	—	
I-5	69	F	?	?										—
I-6	76	F	?	?										—
I-7	85	F	?	?										—
I-8	25*	F												—
I-9	8*	F												—
I-10	12*	M												—

* Persons dead at the time of the investigation.
? Not examined.

ratio was obtained. However, from the results of table 3c it is apparent that the phenylthiocarbamide used was of too weak a concentration, because a 7:3 ratio is usually secured when testing nonrelated persons. Here again a 1:1 ratio was obtained. There are 4 miscarriages recorded, 2 having occurred in

normal women and 2 occurring in affected persons. Only one case of prematurely gray hair was found in the 38 persons of the affected families, and that in a normal individual. Eye color was classified into 2 groups of brown and blue (table 4) and revealed no correlation with this disease. Hair color, color blindness, and midphalangeal hair also appear to be unassociated with hereditary spherocytosis (table 5).

SUMMARY

Nine of the 56 related families studied showed persons with hereditary spherocytosis. Blood smears were obtained from all of these individuals; 18 positive cases were found, and 3 more are possible suspects. The 26 mates of these persons, who permitted blood smears to be made, showed negative results. The data support the conclusion that hereditary spherocytosis is a Mendelian dominant. Evidence indicates that the incidence of the disease is higher in men than in women.

There is suggestive association between the disease, leg ulcers, and gallstones: a well established clinical observation. All of the other characteristics studied proved to be either inconclusive or unassociated with hereditary spherocytosis.

REFERENCES

1. Bell, J. 1935. *On the Types of Progressive Muscular Atrophy.* Treasury of Human Inheritance, Vol. IV, Part II, pp. 95–96. Cambridge, The University Press.
2. Gates, R. R. 1946. *Human Genetics,* Vol. 1, p. 742. New York, The Macmillan Company.
3. Hogben, L. T. 1939. *Nature and Nurture,* p. 143. New York, W. W. Norton Company, Inc.
4. Race, R. R. 1941–1942. On inheritance and linkage relations of acholuric jaundice. (Edited by Fisher, R. A. London, Galton Laboratory for National Eugenics.) *Ann. Eugen.,* Cambr. 11: 365–384.
5. Wolman, I. J. 1945. Congenital hemolytic anemia; review of progress. *Am. J. M. Sc.* 210: 798.

Is Idiopathic Convulsive Disorder Partially Sex-linked?

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FOLLOWING the description by Haldane of partially sex-linked traits in man, Snyder and Palmer published an account of a neurological syndrome which they designated as "idiopathic convulsive disorder." They tentatively localized the gene as being on the homologous segments of the sex chromosomes. The disorder appeared in three sibships descended from two brothers six generations removed. In the sibship which contained three normal males and four affected females the father was related to the mother of the affected children by way of his mother, the ideal situation in which a partially sex-linked gene could descend to four daughters and to none of the sons. There was at least one crossover in the kindred, since a son and daughter were affected in one sibship. Snyder and Palmer state "It thus becomes impossible to make any estimate of the crossover frequency in this pedigree, and, indeed it cannot be insisted that the gene is located on the homologous portions of the sex chromosomes at all." Nevertheless, in his latest text on Principles of Heredity Snyder still places the gene for this disorder on the homologous segment of the sex chromosome, although not specifying its exact location.

It is the purpose of the following note to point out that the crossover frequency can be readily determined from the pedigree, and that the frequency is such as to make it advisable to reconsider locating this gene on the sex chromosomes. Since it is only in the transferral of such a gene by the male parent that the effect of crossing over is noticeable, the number of such crossovers can be directly estimated from Snyder and Palmer's data. Figure 1 is an adaptation of their pedigree, omitting all irrelevant persons, and indicating the sites at which crossing over or non-crossing over must occur if the gene in question is to be transferred from father to child in order to reappear in the 7th generation.

Analysis of the pedigree. Examination of the pedigree shows that there are two brothers in the first generation whose descendants are the affected children in the seventh generation. In VII-4, 6, 7, and 9, the genes are obviously brought down from I-1 through the father and the mother. In VII-1 and 2, they are transmitted from I-1 on the maternal side, and possibly also from the paternal side, since VI-2 bears the same surname as the males in generations III and IV. The manner of relationship, if any, of VI-2 to VI-1 is unknown, hence the

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number of possible crossovers which have occurred to make him a heterozygote cannot be estimated. Finally, VII-12 may have the gene of I-1 duplicated in her, or she may have the genes from I-1 and I-2 present, since her father is descended on his mother's side from I-2 and on his father's side from I-1.

A complete pedigree such as this enables one to estimate the upper and lower limits of the crossover value necessary to produce such a group of affected offspring. First it may be assumed that all the affected children in the seventh generation received their genes from I-1 and that it is purely coincidental that VI-7 was also descended from I-2. This is designated as Pathway I. The gene must have been located on either the X or the Y chromosome in I-1. Table 1-A shows the total number of crossovers and non-crossovers necessary to bring the mutant gene from the X chromosome of I-1 to the seven affected children in the seventh generation. Thus, in order that VII-1 may carry the

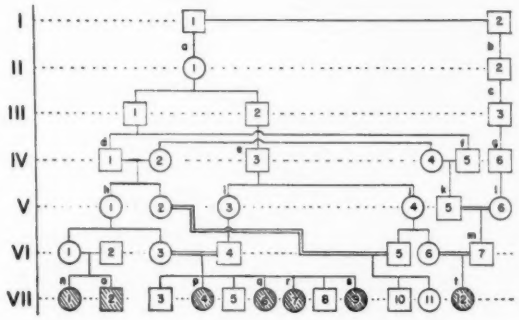

FIG. 1

gene derived from I-1, two crossovers and one non-crossover are essential if we assume the X chromosome of I-1 carried the gene. It takes three crossovers if the gene is on the Y chromosome of I-1. This is based on the assumption that the gene in VI-2 is located on the X chromosome. If it is on the Y chromosome in VI-2 the daughter represents a crossover, the son a non-crossover. Similarly, if the crossovers essential to the production of VII-1 have occurred, it requires two more crossovers and four non-crossovers to produce VII-4, 6, 7 and 9. An additional three crossovers and two non-crossovers give the affected child VII-12. A minimum of eight crossovers and eight non-crossovers is necessary to explain the pedigree, giving a C.O.V. (crossover value) of 50%. Viewing the matings in a similar manner, but assuming that the mutant gene was located on the Y chromosome of I-1 (Table 1-B) one finds that a minimum of nine crossovers and seven non-crossovers must occur in order to produce the affected offspring, a C.O.V. of 56.3%.

Pathway II is the one followed if the assumption is made that the male VI-7 derived his mutant gene from his mother descended from I-2, rather

TABLE 1. ESTIMATION OF CROSSOVER FREQUENCY

Pathway I. Duplication in 7th generation of genes from I-1

A. GENE LOCATED ON X CHROMOSOME OF I-1

Sibship	Path of gene from male parent to offspring	No. crossovers	No. non-cross-overs	Individuals affected
1	I-1 to II-1 through a		1	
	III-1 to IV-1 through d	1		
	IV-1 to V-1 through h	1		
	VI-2 to VII-1* through n		1	VII-1
	VI-2 to VII-2* through o	1		VII-2
2	III-2 to IV-3 through e	1		
	IV-3 to V-3 through i	1		
	VI-4 to VII-4, 6, 7, 9 through p, q, r, s		4	VII-4, 6, 7, 9
3	IV-3 to V-4 through j	1		
	III-1 to IV-5 through f	1		
	IV-5 to V-5 through k		1	
	V-5 to VI-7 through m		1	
	VI-7 to VII-12 through t	1		VII-12
Total.....		8	8	
C.O.V.....		50%		

B. GENE LOCATED ON Y CHROMOSOME OF I-1

Sibship	Path of gene from male parent to offspring	No. crossovers	No. non-cross overs	Individuals affected
1	I-1 to II-1 through a	1		
	III-1 to IV-1 through d	1		
	IV-1 to V-1 through h	1		
	VI-2 to VII-1* through n		1	VII-1
	VI-2 to VII-2* through o	1		VII-2
2	III-2 to IV-3 through e	1		
	IV-3 to V-3 through i	1		
	VI-4 to VII-4, 6, 7, 9 through p, q, r, s		4	VII-4, 6, 7, 9
3	IV-3 to V-4 through j	1		
	III-1 to IV-5 through f	1		
	IV-5 to V-5 through k		1	
	V-5 to VI-7 through m		1	
	VI-7 to VII-12 through t	1		VII-12
Total.....		9	7	
C.O.V.....		56.3%		

* The gene has been assumed to be on the X chromosome of VI-2 in this arrangement. If it were on the Y chromosome of VI-2, there would be a crossover necessary to produce VII-1 and no crossover to produce VII-2. This note applies also to Table 2.

TABLE 2. ESTIMATION OF CROSSOVER FREQUENCY

Pathway II. Duplication in 7th generation of genes from I-1 and I-2

A. GENE LOCATED ON X CHROMOSOMES OF I-1 AND I-2

Sibship	Path of gene from male parent to offspring	No. crossovers	No. non-cross-overs	Individuals affected
1	Same as for Table 1 Part A	2 1	2	VII-1 VII-2
2	Same as for Table 1 Part A	2	4	VII-4, 6, 7, 9
3	I-2 to II-2 through b	1		
	II-2 to III-3 through c		1	
	III-3 to IV-6 through g		1	
	IV-6 to V-6 through l	1		
	VI-7 to VII-12 through t		1	
	IV-3 to V-4 through j	1		
	III-1 to IV-5 through f*		1	VII-12
Total		8	10	
C.O.V.		44.4%		

B. GENE LOCATED ON THE Y CHROMOSOME OF I-1 AND I-2

Sibship	Path of gene from male parent to offspring	No. crossovers	No. non-cross-overs	Individuals affected
1	Same as for Table 1 Part B	3 1	1	VII-1 VII-2
2	Same as for Table 1 Part B	2	4	VII-4, 6, 7, 9
3	I-2 to II-2 through b		1	
	II-2 to III-3 through c		1	
	III-3 to IV-6 through g		1	
	IV-6 to V-6 through l	1		
	VI-7 to VII-12 through t		1	
	IV-3 to V-4 through j	1		
	III-1 to IV-5 through f*		1	VII-12
Total		8	10	
C.O.V.		44.4%		

* Only one possibility at point f is given, it being the minimal number of crossovers or non-crossovers essential to the blocking of the gene from passing through the paternal line of VI-7 to VI-7 himself. Two other possibilities exist.

than from his father V-5. Had the father also carried it, a crossover would have to occur at that point in order to prevent VI-7 from being affected. Table 2-A shows that at least eight crossovers and ten non-crossovers are needed to produce the affected children with the genes being carried on the X chromo-

somes of I-1 and I-2. Eight crossovers and ten non-crossovers are also demanded in order that the requirements be fulfilled when the genes are on the Y chromosomes of the two brothers in the first generation (Table 2-B). Of course, crossovers may occur when the female is transmitting the gene, but the probability of passing the gene on is always ½.

The crossover values, therefore, range from a minimum of 44.4 per cent to a maximum of 56.3 per cent. Although Fisher has presented evidence of the possibility of a crossover value of more than 50 per cent, it would seem unwise to assume this value of 56.3 per cent as valid for this gene on the basis of one isolated pedigree. If all four possibilities are assumed to be equally probable in this kindred, namely that transmission was from I-1 only with the gene located: (1) on the X chromosome; (2) on the Y chromosome; that transmission was through both brothers with the genes: (3) on the X chromosome in both; (4) on the Y chromosome in both, then the sum of all the crossovers is 33 and of the non-crossovers is 35, with the average C.O.V. of 48.5%. With a gene located at this distance from the differential segment, it is impossible to distinguish between partial sex linkage and autosomal inheritance without an extremely large sample. It would seem unwise to invoke partial sex linkage as an explanation merely because one small segment of a pedigree suggests it, when the analysis of the entire pedigree places the site of the gene at a point indistinguishable in this sample from that of autosomal inheritance.

As Table 1 shows, the whole group of affected children are as readily interpreted as having received their duplicate genes from I-1 as from I-1 and I-2. There would still have been a sibship of three unaffected sons and four affected daughters, suggesting partial sex linkage. Combining the values in Parts A and B of Table 1, there are 17 crossovers and 15 non-crossovers essential for the production of this pedigree, giving a C.O.V. of 53.1%. This is quite different from the C.O.V. of 0 that the isolated sibship alone suggests. Snyder and Palmer state that "The peculiar sex distribution of the trait in the family of the propositus, however, coupled with the fact that the parents are related in precisely the manner that would be necessary to produce this particular sex distribution of an incompletely sex-linked gene, make it a reasonable inference that the gene is located on the homologous portions of the X and Y chromosomes". It must be pointed out that although finding all daughters affected and all sons normal in a family of four daughters and three sons is unusual, it could be expected to occur once in every 35 families of three boys and four girls, even were the gene on an autosome.

The next point is that with the large probability that these affected children all derived their mutant gene from I-1, the inference that it is sex linked is not as reasonable as that it is autosomal. With a C.O.V. of 53.1% and given a family of three boys and four girls, one would have expected this peculiar

distribution of the defect *less often* were the gene partially sex linked than if it were on an autosome.

Up to this point, I have dealt with the pedigree in its entirety, since if the gene is partially sex linked in one sibship it must of necessity be similarly linked in all parts. In sibship 1, however, we do not know how many crossovers, if any, were essential to have the gene present in VI-2, because we cannot be sure that VI-2 derived his gene from this line. We can only calculate the number of crossovers necessary to have the gene descend from I-1 to VI-1 assuming that the gene did so descend with no mutation between I-1 and VI-1 to account for the defect in VII-1 and 2. Similarly, in sibship 3, we cannot say whether VI-7 derived his mutant gene from his father or his mother, and so cannot calculate *exactly* the number of crossovers necessary to produce VII-12; we can only estimate two values equally probable. With respect to sibship 2, however, the only reasonable probability is that both the parents who are related, derived their mutant gene from I-1. For this sibship, therefore, which is the one which suggested partial sex-linkage, the crossover value can be directly calculated. Since sibships 1 and 3 are to be omitted from the discussion for reasons above stated, the number of crossovers necessary to produce sibship 2 must begin with I-1, the common ancestor of the two heterozygous parents VI-3 and VI-4. If the gene is on the X chromosome of I-1, there must be crossovers at d, h, e and i, and no crossovers at a, p, q, r, s, or four crossovers and five non-crossovers. If the gene is on the Y chromosome of I-1, there must be crossovers at a, d, h, e, i, and none at p, q, r, s; or a total of five crossovers and four non-crossovers. The average value for crossovers for the only sibship in which the minimal number essential can be calculated, is, therefore, 50 per cent, indistinguishable from random assortment of the genes determining the trait and sex.

Two more possibilities exist, although they are less probable than those already mentioned. It may be that the parents of I-1 and I-2 were related, and that each was a heterozygote, so that I-1 may have had the mutant gene on his X, and I-2 on his Y chromosome, or vice versa. If the first of these possibilities is correct, (and of courth Pathway II must be involved in such a situation), the total number of crossovers would be seven, and of non-crossovers eleven; with a C.O.V. of 38.8%. If the second possibility were true, there would be nine crossovers and an equal number of non-crossovers, making a C.O.V. of 50%. The average C.O.V. for both these possibilities would be 44.4%. These two possibilities were included merely to make the analysis of the four possible sites of the genes on the chromosomes complete, XX, YY, XY and YX. There is no need to invoke the latter two possibilities, since they go beyond the range of the pedigree; the other possibilities tabulated keep strictly within known limits.

SUMMARY

The pedigree of idiopathic convulsive disorder reported by Snyder and Palmer for which partial sex-linkage was suggested as the mode of inheritance is reviewed. It is possible to determine the minimal crossover percentages necessary to produce such a pedigree if partial sex-linkage is involved. The average C.O.V. is shown to be 48.5, with a minimum of 44.4 and a maximum of 56.3 per cent. One method of interpretation of the pedigree, namely, that all the affected derived their mutant gene from one man, which is equally as probable as the alternative interpretation that two brothers were involved, gives a C.O.V. of 53.1 per cent. The one sibship which suggested partial sex-linkage shows, on closer inspection, that the average minimal number of crossovers necessary to produce these affected children is equal to the average minimal number of non-crossovers necessary. It is suggested, therefore, until more evidence is forthcoming to substantiate the localization of this gene on the homologous segments of the sex chromosome, that it be considered as exhibiting autosomal recessive inheritance.

REFERENCES

1. Fisher, R. A., Lyon, M. F. & Owen, A. R. G. 1947. The sex chromosome in the house mouse. *Heredity* 1: 355–366.
2. Haldane, J. B. S. 1936. Search for incomplete sex-linkage in man. *Ann. Eugen.* 7: 28–57.
3. Snyder, L. H. & Palmer, D. M. 1943. Idiopathic convulsive disorder with deterioration apparently dependent upon incompletely sex-linked gene. *J. Hered.* 34: 207–212.

A New Rare Rhesus Agglutinogen

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CORRESPONDING to the three Rh factors, Rh_0, rh′ and rh″, three reciprocally related Hr factors are theoretically possible (Wiener, 1945), of which two, hr′ and hr″, have actually been found (Levine, 1943; Race and Taylor, 1943; Wiener et al., 1945, Mourant, 1945; Wiener and Peters, 1948). Until recently, tests on large random series of blood specimens from Caucasoids as well as family studies appeared to confirm the hypothesis that the blood factor pairs rh′-hr′ and rh″-hr″ are reciprocally related, and behave serologically and genetically like the blood factor pair M-N. Thus, among Caucasoids, blood lacking the rh′ factor invariably contained the hr′ factor, while blood lacking the hr′ factor always contained the rh′ factor (Wiener et al., 1945; Wiener, 1946; Race et al., 1948; Wiener and Gordon, 1951). Moreover, rh′-negative parents had no hr′-negative children, and parents who were hr′ negative had no rh′-negative children (Wiener et al., 1949; Lawler et al., 1951). Similar statements appeared to hold for the factor pair rh″-hr″, but not as many blood specimens have been tested for the hr″ factor (Wiener et al., 1949; Lawler et al., 1951; Race and Sanger, 1950; Wiener, 1950).

Recently, Race et al. (1951) encountered a blood specimen which gave atypical reactions in the Rh-Hr tests. The blood specimen came from a healthy woman, whose serum was found to agglutinate 1400 random blood specimen but did not agglutinate her own cells. She had never received a blood transfusion or blood injection, but her third child had died of erythroblastosis. While the patient's red cells exhibited no unusual reactions outside the Rh-Hr system, the rhesus phenotype was most unusual. The patient's cells proved to contain the Rh_0 factor, but lacked the rh′, rh″, hr′ and hr″ factors. A sample of this blood specimen was kindly sent to us by Drs. Race and Selwyn, and we were able to confirm these findings with the reagents at our disposal.

The discovery of the atypical Rh-Hr agglutinogen described by Race et al. suggests the possible existence of additional related variants of the rhesus agglutinogens. The purpose of the present report is to describe a new rhesus agglutinogen, somewhat similar to the one found by Race et al., which we encountered in the course of routine Rh-Hr typings on blood specimens from Negroids.

MATERIALS AND METHODS

The blood specimens studied came from a series of 743 Caucasoids and 248 Negroid individuals in New York City. The 743 Caucasoids were all professional blood donors. The

248 Negroids were individuals involved in disputed paternity proceedings in the Court of Special Sessions of New York City. (There was also a comparable larger series of 753 Caucasoids who were similarly involved in paternity proceedings, but these were not used for the statistical analysis.) They had denied paternity of the complainant's child, and their blood types were determined in the course of the routine medicolegal examinations. In order that the statistical analysis include only unrelated individuals, the blood specimens from the babies are not included in the present study.

The blood specimens of the professional donors which are used in this study were tested between May, 1950 and October, 1951. Each sample was tested with the following antisera: anti-Rh_0, -rh′, -rh″, -rh^w, -hr′, and -hr″. The blood specimens from the individuals involved in paternity proceedings were tested during the period from September, 1948 to May, 1952. Most of the latter blood specimens were also tested with the six Rh-Hr antisera, except on occasions when there was a shortage of the rarer sera, anti-rh^w and anti-hr″. The tests were carried out by the tube agglutination method. All blood specimens giving negative reactions with anti-Rh_0 tube test agglutinating serum, were further tested by the slide method with strong conglutinating anti-Rh_0 serum. All blood specimens giving negative reactions with anti-hr′ agglutinating serum were retested with an anti-hr′ conglutinating serum. Those rare blood specimens giving negative reactions with the anti-hr″ serum or positive reactions with anti-rh^w serum were retested several times, by using them as controls in tests carried out on succeeding days. In a number of cases, the absence of the hr″ factor from a blood specimen was verified by the absorption technique.

In order to economize with the rare anti-rh^w serum,[1] this reagent was salvaged after each test and re-used several times, as described in a previous paper (Wiener and Gordon, 1949). The anti-hr″ serum which we used in the present study came from a woman with hemolytic anemia, and has been described by Wiener and Peters (1948). She was bled at intervals of approximately six months, and since the hr″ antibody titer generally fell with the passage of time, she was restimulated 7 to 10 days before each bleeding by an intravenous injection of a small amount of group O, type rh blood. The most recent specimen obtained from this patient had an anti-hr″ titer of approximately 80 units by the saline tube agglutination method. The serum also contained a potent autoantibody of approximately 100 units titer at body temperature for enzyme-treated human cells (including the patient's own red cells). The autoantibodies did not clump human cells by the conglutination or antiglobulin methods; and the direct antiglobulin test for coating of the patient's cells by autoantibodies was negative. Since the autoantibodies did not clump unmodified red cells, it did not interfere with the tests for the hr″ factor. In order not to waste this rare antiserum, it was diluted 1 to 5 with saline solution and the tests were carried out in narrow tubes (inside diameter 4 mm.). All blood cells giving negative reactions were retested with the full strength serum. Unfortunately, the patient who had supplied the anti-hr″ serum recently died of pneumonia, and at autopsy, unexpectedly, a right mitral stenosis was found.

RESULTS

In table 1 are shown the results of the Rh-Hr typings on the series of 743 professional blood donors. All the blood specimens gave the expected reactions with the six antisera, and the distribution of the types is similar to that observed in our previous studies except for a somewhat higher percentage of type rh individuals. There were 14 blood specimens (1.9 per cent) which were ag-

[1] The anti-rh^w serum used in this study was kindly provided by Dr. J. J. van Loghem, Jr., to whom the authors wish to acknowledge their indebtedness.

glutinated by anti-rh^w serum, and one blood specimen of the rare type Rh_zRh_1. Only 11 blood specimens were not agglutinated with anti-hr″ serum, and all these were of the type Rh_2. There was not a single blood specimen which lacked both blood factors of either of the pairs rh′-hr′ and rh″-hr″. The reactions with anti-hr″ serum were strong except for many blood specimens of type Rh_z (Rh_1Rh_2). The latter could not be ascribed merely to a "gene-dose" effect, because the blood specimens of type Rh_2rh, which likewise have only a single dose of the hr″ factor, almost invariably gave strong reactions with the anti-hr″ serum. Possibly there was some interference from the rh′ factor present

TABLE 1. DISTRIBUTION OF Rh-Hr TYPES IN A SERIES OF 743 CAUCASOIDS*

PHENOTYPES	NUMBER OF INDIVIDUALS	PER CENT	PHENOTYPES FURTHER SUBDIVIDED BY rh^w ANTISERUM		
			Phenotypes	Number	Per cent
Rh_0	18	2.42			
Rh_1 Rh_1rh	241	32.50	Rh_1rh	237	31.96
			Rh_1^wrh	4	0.54
Rh_1Rh_1	143	19.24	Rh_1Rh_1	135	18.17
			$Rh_1^wRh_1$	8	1.07
Rh_2 Rh_2rh	90	12.11			
Rh_2Rh_2	11	1.47			
Rh_z Rh_zRh_0	96	12.92	Rh_zRh_0	94	12.65
			$Rh_z^wRh_0$	2	0.27
Rh_zRh_1	1	0.13			
rh	138	18.55			
rh′ rh′rh	3	0.40			
rh″ rh″rh	2	0.26			
Totals	743	100.00	rh^w pos.	14	1.88

* All specimens were tested with sera anti-Rh_0, -rh′, -rh″, -rh^w, -hr′, and -hr″.

in type Rh_1Rh_2 blood, and absent from type Rh_2 blood. This would be comparable to the considerably weaker reaction of group A_2B blood with anti-A serum, as compared with group A_2 blood.

The findings on the smaller series of Negroid blood specimens are shown in table 2. The distribution of types is similar to that observed in our previous studies (Wiener et al., 1943; 1944) and again demonstrate the high percentage of individuals of type Rh_0. Another striking feature is the occurrence of blood specimens giving atypical reactions with anti-Rh_0 serum (Rh_0 variants), again in conformity with our earlier observations (Wiener et al., 1950). The findings on Negroids confirm the reciprocal relationship between factors rh′ and hr′. Only 9 blood specimens failed to react with anti-hr′ serum; 8 of these were of individuals of type Rh_1 and one from an individual of type Rh_1Rh_2. The latter individual, whose phenotype was Rh_zRh_1 and who was therefore presumably a carrier of the R^z gene, was a Puerto-Rican.

On the other hand, the reactions of the blood specimens from Negroids with anti-hr″ serum exhibited certain irregularities in contrast to the blood specimens from Caucasoids. There were as many as 8 blood specimens giving weak or doubtful reactions, and 5 of these were from individuals of type Rh_1rh and

TABLE 2. RESULTS OF TESTS FOR hr″ FACTOR ON A RANDOM SERIES OF BLOOD SPECIMENS FROM NEGROIDS

PHENOTYPE*	NUMBER† OF INDIVIDUALS	PER CENT	REACTIONS WITH ANTI-hr″ SERUM			
			Positive	Negative	Doubtful	Not tested
Rh_0	114	40.14	68	1	4	41
Rh_1rh	75	26.41	41	0	1	33
$Rh_1^{\gamma}rh$	1	0.35	1	0	0	0
Rh_1Rh_1	8	2.82	6	0	0	2
Rh_2	47	16.55	36	4	3	4
Rh_z (hr′ pos.)	9	3.17	7	0	0	2
Rh_z (hr′ neg.)	1	0.35	0	0	0	1
rh	17	5.99	11	0	0	6
rh′rh	2	0.70	2	0	0	0
rh″	1	0.35	1	0	0	0
Rh_0 variants	9	3.17	6	0	0	3
Totals	284	100.0	179	5	8	92

* All blood specimens were tested with anti-Rh_0, -rh′, -rh″, -rh^w, and -hr′ serum.
† Includes 23 Puerto-Ricans.

TABLE 3. FAMILY STUDY ON A PUERTO-RICAN WOMAN WITH BLOOD OF TYPE Rh_0 LACKING FACTOR hr″

BLOOD OF	A-B-O GROUP	M-N TYPE	rh-Hr PHENOTYPE*	REACTION WITH ANTI-hr″ SERUM†
Putative father	O	MN	Rh_1rh	++±
Mother	B	M	Rh_0	−
1st child	B	M	Rh_1rh	+±
2nd child	O	MN	Rh_0	++±

* Based on reactions with anti-Rh_0, -rh′, -rh″, -hr′ sera.
† The intensity of the reactions is indicated by the number of plus signs as follows: +++, one large clump; ++±, several large clumps; ++, many smaller clumps easily visible to the naked eye; +±, numerous smaller clumps just visible to the naked eye; +, clumping distinct but visible only under low power of microscope; ±, doubtful reaction; −, cells separate and distinct microscopically.

type Rh_0, who theoretically should have a double dose of the hr″ factor. In addition, there were 5 other blood specimens giving entirely negative reactions with the anti-hr″ serum. Four of the latter were from individuals of type Rh_2, but one was a blood specimen of type Rh_0 from a Puerto-Rican woman. Since blood of type Rh_0 is supposed to have a double dose of the hr″ factor, this blood specimen was subjected to a thorough study. By absorption tests, it was possible to confirm the absence of the factor hr″ from the blood specimen. More-

over, the individual was recalled and a fresh venous sample was obtained and retested with the full strength anti-hr″ serum. Again it was possible to show that the blood cells contained factors Rh_0 and hr′, but not factors rh′, rh″, or hr″. Thus, for this individual, the reciprocal relationship between factors rh″ and hr″ does not hold, and her blood is similar in that regard to the one described by Race and Selwyn.

In table 3 is presented an analysis of the Rh-Hr reactions of the two children of the woman with atypical Rh_0 blood lacking hr″ factor, in order to show the reactions with anti-hr″ serum of the blood cells of these two children. One child belongs to type Rh_0 like the mother, but his blood reacts typically with anti-hr″ serum; the blood of the second child who belongs to type Rh_1rh is also agglutinated by the anti-hr″ serum, but the reactions are only of moderate intensity. The putative father could not be excluded by the blood tests (cf. table 3), but of course this does not necessarily mean that he is actually the father of the two children. To explain the failure of the mother's blood to agglutinate in anti-hr″ serum, one must postulate that her blood contains a special kind of Rh agglutinogen, which may be designated Rh_0^u in order to indicate the presence of the hr′ factor but the absence of the hr″ factor.[2] This individual is presumably homozygous for the corresponding gene R^{ou}, while each of the two children therefore have at least a single dose of the gene.

The existence of individuals with red cells lacking both factors rh″ and hr″ has an important implication for the medicolegal application of these tests in cases of disputed parentage. If atypical agglutinogens like Rh_0^u and Rh_0^x are not taken into account, this could lead to erroneous exclusions of parentage. In fact, two instances were encountered by us in the series of Negroids involved in disputed paternity proceedings, which might have been misinterpreted in this manner. As shown in table 4, in both these cases the mother's blood reacted as type Rh_0, while the child's blood gave reactions corresponding to type Rh_2Rh_2; that is, in these two families, the mother's blood was rh″ negative while her child's blood was hr″ negative, contradicting the postulated reciprocal relationship between factors rh″ and hr″. The findings are readily explained if one assumes that these two mothers are carriers of the rare gene R^{ou}, and that the two children are both of the genotype R^2R^{ou}. It is significant that the blood of one of the mothers gave only weak reactions with anti-hr″ serum suggesting the presence of hr″ factor in single dose.

Thus, among the fewer than 300 Negroid individuals tested with anti-hr″

[2] In the very first study on the heredity of the Rh blood types (Wiener et al., 1944) the letters "U" and "V" were used to represent the factors rh′ and rh″, respectively. Accordingly, the small letters "u" and "v" could be used for factors hr′ and hr″. Therefore, when type Rh_0 blood is found to contain hr′ factor but to lack hr″ factor, as in the case described here, we indicate this by the superscript "u", namely Rh_0^u. The superscript "v" will be used, on the other hand, for hypothetical blood of type Rh_0 possessing factor hr″ but lacking factor hr′. When type Rh_0 blood lacks both Hr factors the superscript "x" will be used, e.g., the blood described by Race et al. is designated Rh_0^x.

serum, individuals presumably carrying the gene R^{ou} were detected three times, and one of these three individuals was homozygous for the gene. No doubt the number of individuals in this series carrying the R^{ou} gene was actually considerably larger, but the types of mother and child were not always favorable for demonstrating the presence of the gene. At any rate, the gene appears to be not uncommon among Negroids. On the other hand, as shown in table 1, the gene is rare among Caucasoids, if it occurs at all. In this connection, the second series of 753 Caucasoids (involved in disputed paternity proceedings) has been analyzed; of these, 563 individuals were tested with anti-hr″ serum. Thirteen persons were encountered with blood lacking the hr″ factor; all of them belonged to type Rh_2. As has already been mentioned, weak reactions with anti-hr″ serum are not uncommon among individuals of type Rh_1Rh_2.

TABLE 4. TWO EXAMPLES OF ATYPICAL Rh-Hr REACTIONS IN MOTHER AND CHILD, EXPLAINED BY POSTULATING THE PRESENCE OF GENE R^{ou}

BLOOD OF	A-B-O GROUP	M-N TYPE	rh-Hr TYPE	REACTION WITH ANTI-hr″ SERUM	PROBABLE GENOTYPE
Putative father.....	A_1	M	Rh_xRh_0	++	R^1R^2
Mother.....	A_1	MN	Rh_0	++	$R^{ou}r$ or $R^{ou}R^o$
Child.....	A_1	M	Rh_2Rh_2	−	R^2R^{ou}
Putative father.....	A_1	MN	Rh_2rh	++	R^2r or R^2R^o
Mother.....	B	MN	Rh_0	±	$R^{ou}r$ or $R^{ou}R^o$
Child.....	O	M	Rh_2Rh_2	−	R^2R^{ou}

In addition, five individuals of type Rh_1Rh_1 and one of type Rh_1rh unexpectedly gave weak reactions with the anti-hr″ serum. Since these were not further tested, they may represent accidental technical deviations, but even if one assumes the presence of an R^{ou} gene, it is evident that this gene is but rarely present among Caucasoids in comparison to Negroids. Since at least among Negroids the postulated reciprocal relationship between the rh″ and hr″ factors does not always hold, the anti-hr″ serum may be used in medicolegal cases of disputed parentage only with certain reservations. Thus, only when the accused man belongs to type rh or rh′ and the child to type Rh_2Rh_2, or when the accused man belongs to type Rh_2Rh_2 and the child to type rh or rh′, would it be safe to conclude that the paternity is excluded, because then the question of the rare R^{ou} gene would not arise.

The situation with regard to the factor pair rh′-hr′ is more satisfactory, as far as the medicolegal application is concerned. Not a single exception to the theory has been encountered in our extensive series of families, nor has any been found by Race and his coworkers. However, the discovery by Race and Selwyn of the rare individual of type Rh_0^x indicates that such exceptions may actually exist. This theoretical, rare possibility should not prevent the use of

the Rh-Hr tests in cases of disputed parentage, but it does perhaps call for some mild qualification when the rh′-hr′ tests exclude an accused man. On the other hand, no qualification is necessary for the dominance rule of inheritance of the various Rh-Hr factors.

COMMENT

While studying the serological behavior of the blood from the individual of type Rh_0^x (—D—), Race et al. observed an unexpected phenomenon. In tests with blocking anti-Rh_0 sera, it was found that clumping occurred also in saline media with most such antisera. Race et al. conclude "The curious ability of these cells to be agglutinated in saline by incomplete anti-D suggests that the incomplete antibody is not monovalent as it is so frequently represented. It suggests rather that some hindrance to agglutination in saline by incomplete anti-D is removed when all C and E antigens are absent from the cells."

We have been able to confirm the report regarding this anomalous behavior of the Rh_0^x blood in tests with blocking anti-Rh_0 serum, but we cannot agree with Race's interpretation (cf. Sturgeon, 1952). A long time ago, we noticed that there is a reciprocal relationship between the agglutinability of Rh-positive red cells by anti-Rh sera and the ease with which they are blocked by Rh_0 univalent antisera. For example, old cell suspensions give lower titers in conglutination and agglutination tests, but higher titers in titrations carried out by the blocking technique. On the other hand, fresh cells homozygous for the Rh_0 factor generally give higher titers by the conglutination and agglutination methods and lower titers by the blocking technique. Almost all Rh_0 antisera contain a mixture of the univalent and bivalent forms of the antibody. In fact, many so-called "pure" blocking or "incomplete" Rh_0 antisera actually contain a certain amount of anti-Rh_0 agglutinin, which is masked by the more potent blocking antibody. With highly agglutinable cells such as the homozygous Rh_0^x (—D—/—D—) cells of Race et al., the hidden Rh_0 agglutinin will cause clumping of cells in tests carried out in saline media despite the presence of Rh_0 blocking antibody. This, in fact, is an important source of error in Rh-Hr blood typing, since most anti-rh′ and anti-rh″ reagents contain anti-Rh_0 blocking antibody. In tests against homozygous bloods of type Rh_0, which are not uncommon among Negroids, such reagents may give weak clumping in tests carried out in saline media. If the true nature of these reactions is not recognized, such blood specimens may be incorrectly classified as type Rh_1, Rh_2, or Rh_1Rh_2 instead of type Rh_0.

The Fisher-Race school have committed themselves to the theory that the Rh-Hr factors are inherited in threes by means of corresponding triply linked genes. The present observations provide further evidence refuting this concept. Unfortunately, instead of modifying their theory to conform with the observations, British workers have chosen to attempt to force the facts to fit their

preconceived ideas. They apparently are not disturbed by their inability to procure anti-Hr_0 (d) serum, or by the existence of agglutinogens such as Rh_1^w with four Rh-Hr blood factors instead of three (cf. table 5). To account for the agglutinogen Rh_0^x with but a single Rh-Hr factor, they have been compelled to postulate a deletion involving so-called gene pairs *C-c* and *E-e*. Similarly, no doubt, to account for the observations reported here, they will postulate a deletion involving the so-called gene pair *E-e*. On the other hand, if one takes into account the distinction between blood factor and agglutinogen and adopts the concept of inheritance by multiple allelic genes, one avoids the

TABLE 5. PRESENT STATUS OF THE Rh SERIES OF ALLELIC GENES

GENE	CORRESPONDING AGGLUTINOGEN	BLOOD FACTORS PRESENT	REMARKS	INCIDENCE
1. r	rh	hr′ and hr″	Only 2 factors demonstrable	One of most common Rh genes in Caucasoids. Less common in Negroids. Rare or absent in Mongoloids
2. r'	rh′	rh′ and hr″	Only 2 factors demonstrable	Rare gene
3. r''	rh″	rh″ and hr′	Only 2 factors demonstrable	Rare gene
4. r^y	rh_y	rh′ and rh″	Only 2 factors demonstrable	Extremely rare gene
5. R^0	Rh_0	Rh_0, hr′, and hr″		Most common gene among Negroids; relatively uncommon in Caucasoids and Mongoloids
6. R^1	Rh_1	Rh_0, rh′, and hr″		Most common gene in Mongoloids; common also in Caucasoids and Negroids
7. R^2	Rh_2	Rh_0, rh″ and hr′		Relatively common gene in all races
8. R^z	Rh_z	Rh_0, rh′ and rh″		Very rare gene in Caucasoids and Negroids; less rare in Mongoloids
9. R^{1w}	Rh_1^w	Rh_0, rh′, rh^w and hr″	4 blood factors demonstrable	Relatively uncommon gene
10. $\mathfrak{R}^0$	$\mathfrak{R}h_0$	$\mathfrak{R}h_0$, hr′ and hr″		Rare in Caucasoids; more common in Negroids
11. $\mathfrak{R}^1$	$\mathfrak{R}h_1$	$\mathfrak{R}h_0$, rh′, and hr″		Rare in Caucasoids; more common in Negroids
12. $\mathfrak{R}^2$	$\mathfrak{R}h_2$	$\mathfrak{R}h_0$, rh″ and hr′		Rare in Caucasoids; more common in Negroids
13. R^{ou}	Rh	Rh_0 and hr′	Only 2 factors demonstrable	Rare gene present in Negroids; not yet found in Caucasoids
14. R^{oz}	Rh_0^x	Rh_0	Only a single blood factor demonstrable	Extremely rare agglutinogen in Caucasoids

necessity of resorting to such far-fetched supplementary assumptions. (cf. Wiener and Wexler, 1952).

SUMMARY

A new rhesus agglutinogen is described which is characterized by the presence of blood factors Rh_0 and hr′ and the absence of blood factors rh′, rh″, and hr″. This agglutinogen is not uncommon among Negroids but has so far not been encountered among Caucasoids. A simple method of designating the new agglutinogen as well as the related agglutinogen reported by Race et al. is proposed. The implications of the observations for the serology and genetics of the Rh-Hr types are discussed, and especially the effect on the medicolegal application of the tests in cases of disputed parentage.

REFERENCES

LAWLER, S. D., BERTINSHAW, D., SANGER, R., & RACE, R. R. 1951. Inheritance of the *Rh* blood groups; 150 families tested with anti-C-c-C^w-D-E and anti-e. *Ann. Eugen.* LOND. 15: 258–270.

LEVINE, P. 1943. The pathogenesis of erythroblastosis fetalis. *J. Pediat.* 23: 656–675.

MOURANT, A. E. 1945. A new rhesus antibody. *Nature* LOND., 155: 542.

RACE, R. R., MOURANT, E. E., LAWLER, S. D., & SANGER, R. 1948. The Rh chromosome frequencies in England. *Blood*, 3: 689–695.

RACE, R. R., & SANGER, R. 1950 *Blood Groups in Man.* Blackwell Scientific Publ., Oxford.

RACE, R. R., SANGER, R., & SELWYN, J. A. 1951. A possible deletion in a human Rh chromosome; a serological and genetical study. *Brit. J. Exp. Path.*, 32: 124–135.

RACE, R. R., & TAYLOR, G. L. 1943. A serum that discloses the genotype of some Rh-positive people. *Nature* (Lond.), 152: 300.

STURGEON, P. 1952. Studies on a "complete" and an "incomplete" Rh antiserum with cDe/cde and -D-/-D- cells. I. The native sera. *J. Immunol.*, 68: 277–285.

WIENER, A. S. 1945. Theory and nomenclature of the Hr blood factors. *Science*, 102: 479–482.

WIENER, A. S. 1946. Recent developments in the knowledge of the Rh-Hr blood types; tests for Rh sensitization. *Am. J. Clin. Path.*, 16: 477–497.

WIENER, A. S. 1950. Blood grouping in disputed parentage with special reference to the Rh-Hr blood types. *Proceedings of the International Society of Hematology*, 207–220, Grune and Stratton, N. Y. C.

WIENER, A. S., BELKIN, R. B., & SONN, E. B. 1944. Distribution of the A_1-A_2-B-O, M-N, and Rh blood types among negroes in New York City. *Am. J. Phys. Anthrop.*, 2 (N.S.): 187–194.

WIENER, A. S., DAVIDSOHN, I., & POTTER, E. L. 1945. Heredity of the Rh blood types. II. Observations on the relation of factor Hr to the Rh blood types. *J. Exp. Med.*, 81: 63–72.

WIENER, A. S., & GORDON, E. B. 1949. Studies on the blood factor rh^w. *Amer. J. Clin. Path.*, 19: 621–629.

WIENER, A. S., & GORDON, E. B. 1951. Repartition des facteurs de groupes sanguine dans une population de New York City. *Rev. d'Hématol.*, 6: 46–50.

WIENER, A. S., GORDON, E. B., & HANDMAN, L. 1949. Heredity of the Rh blood types.

VIII. Additional family studies with special reference to factor rh^w. *Am. J. Human Genet.*, 1: 127–140.

WIENER, A. S., & PETERS, H. R. 1948. Intragroup incompatibility due to the hr″ factor. *Am. J. Clin. Path.*, 18: 533–536.

WIENER, A. S., SONN, E. B., & BELKIN, R. B. 1943. Heredity and distribution of the Rh blood types. *Proc. Soc. Exp. Biol.* 54: 238–240.

WIENER, A. S., SONN, E. B., & BELKIN, R. B. 1944. Heredity of the Rh blood types. *J. Exp. Med.* 79: 235–253.

WIENER, A. S., UNGER, L. J., & SONN, E. B. 1945. New data on the distribution of the Rh blood types. *Proc. Soc. Exp. Biol.* 58: 89–92.

WIENER, A. S., & WEXLER, I. B. 1952. The mosaic structure of red blood cell agglutinogens. *Bact. Rev.* 16: 69–87.

A Further Note on the Genetics of Psoriasis

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IN a recently published paper the present authors suggested, with tongue in cheek, that a formal explanation of the data could be obtained by assuming that psoriatic patients were homozygous for two unlinked autosomal recessive genes (Steinberg and associates, 1951). The following analysis may indicate that the hypothesis is not so farfetched as we at first thought.

If it is assumed that psoriatics are *aabb*, that is, homozygous recessive for a pair of nonlinked genes, and that p and r equal the frequency of a and b respectively and $(1 - p) = q =$ the frequency of A and $(1 - r) = s =$ the frequency of B, it is possible to derive an estimate of the relative frequencies with which none, one, or both parents of randomly selected psoriatics should be psoriatic. It is possible also to obtain an estimate of the ratio of the frequency of psoriasis among the sibs of psoriatic patients when one parent is psoriatic to that obtained when neither is psoriatic. The calculations are given in table 1.

Let $$pr = m \text{ and } 1 - pr = n$$

Then from column 3 of table 1 the frequencies of the three types of matings are as in table 2. The maximum likelihood solution for m gives $m = (2a + b)/2T$ which equals the frequency of psoriasis among the parents = 0.0593.

Table 3 shows a comparison of the observed versus the expected values.

The frequency of affected sibs when one parent and when either parent is psoriatic may be derived from the totals of columns 1 and 2 as in table 4.

The ratio of the two frequencies (1 parent psoriatic: 0 parent psoriatic)

$$= \frac{1 - pr}{2(q + s)} \cdot \frac{4(q + s)^2}{(1 - pr)^2} = \frac{2(q + s)}{(1 - pr)}$$

The values of q and s are unknown; however, an estimate of $pr = 0.0593$ is available. Hence p may be taken as $0.0593/r$, and $q + s = 2 - p - r =$

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TABLE 1. ANALYSIS OF MATINGS WHICH YIELD PSORIATIC OFFSPRING

MATING	1 f	2 FREQUENCY OF RECESSIVES IN THE TOTAL POPULATION	3 = 2/p^2r^2 PROPORTION OF RECESSIVES DERIVED FROM GIVEN MATING
Both parents psoriatic			
$aabb \times aabb$	p^4r^4	p^4r^4	p^2r^2
One parent psoriatic			
$aabb \times Aabb$	$4p^3qr^4$	$2p^3qr^4$	$2pqr^2$
$\times aaBb$	$4p^4r^3s$	$2p^4r^3s$	$2p^2rs$
$\times AaBb$	$8p^3qr^3s$	$2p^3qr^3s$	$2pqrs$
Total	$4p^2r^3(q+s)$	$2p^3r^3(1-pr)$	$2pr(1-pr)$
No parents psoriatic			
$Aabb \times Aabb$	$4p^2q^2r^4$	$p^2q^2r^4$	q^2r^2
$\times aaBb$	$8p^3qr^3s$	$2p^3qr^3s$	$2pqrs$
$\times AaBb$	$16p^3q^2r^3s$	$2p^2q^2r^3s$	$2q^2rs$
$aaBb \times aaBb$	$4p^4r^2s^2$	$p^4r^2s^2$	p^2s^2
$\times AaBb$	$16p^3qr^2s^2$	$2p^3qr^2s^2$	$2pqs^2$
$AaBb \times AaBb$	$16p^2q^2r^2s^2$	$p^2q^2r^2s^2$	q^2s^2
Total	$4p^2r^2(q+s)^2$	$p^2r^2(1-pr)^2$	$(1-pr)^2$

TABLE 2. FREQUENCIES OF TYPES OF MATING

	EXPECTED	OBSERVED
Both parents psoriatic	m^2	a
One parent psoriatic	$2mn$	b
Neither parent psoriatic	n^2	c

TABLE 3. OBSERVED VERSUS EXPECTED VALUES

NUMBER OF PSORIATIC PARENTS	NUMBER OF PATIENTS WITH GIVEN NUMBER OF PSORIATIC PARENTS	
	Expected	Observed
2	1.6	0
1	51.8	55
0	410.6	409
Total	464.0	464

$X^2_{(1)} = 1.814$ $p > 0.10$.

TABLE 4. FREQUENCY OF AFFECTED SIBS

NUMBER OF PARENTS PSORIATIC	FREQUENCY OF PSORIATIC SIBS
1	$\frac{2p^3r^3(1-pr)}{4p^2r^2(q+s)} = \frac{1-pr}{2(q+s)}$
0	$\frac{p^2r^2(1-pr)^2}{4p^2r^2(q+s)^2} = \frac{(1-pr)^2}{4(q+s)^2}$

$2 - (0.0593/r) - r$. The expression is a maximum when $r = \sqrt{0.0593} = 0.24 = p$.

Hence the maximum value of the foregoing ratio is $2(0.76 + 0.76)/[1 - (0.0593)] = 3.23$. The observed frequency of affected sibs of patients with one parent psoriatic was 0.09 (18/200) and with neither parent psoriatic, 0.0245 (40/1,630). Their ratio (R) equals 3.67 ± 0.84.* The difference between the observed and expected values equals 0.52σ and $P \leqq 0.6$.

Surprisingly, therefore, by both portions of the test the data are in agreement with the expected frequencies derived from the two-gene hypothesis.

We should like to reiterate that we do not think we have proved the hypothesis. We have merely made it more likely.

REFERENCE

1. Steinberg, A. G., Becker, S. W., Jr., Fitzpatrick, T. B. & Kierland, R. R.: A Genetic and Statistical Study of Psoriasis. *Am. J. Human Genet.* 3: 267–281 (Sept.) 1951.

* The standard error was calculated on the basis of the observed frequencies. If the theoretical frequencies are used the standard error equals 0.44 and $P \cong 0.3$.

BOOK REVIEWS

The Measurement of Linkage in Heredity

By K. MATHER (Dept. of Genetics, University of Birmingham, Eng.) New York: John Wiley & Sons, Inc., Second Edition, 1951. Pp. 149. $1.75.

THIS monograph presents some of the mathematical techniques which may be used in measuring linkage. Most plant and animal geneticists will find the discussions of planning and analysis of experiments helpful. The demonstrations of the use of X^2 are clear, and the many special formulae are useful.

The human geneticist will find three chapters, about one quarter of the book, devoted particularly to his problems. The first of these chapters deals with the problem of determining the likelihood that a particular condition is the manifestation of a homozygous recessive gene. This chapter is concluded with a X^2 test of heterogeneity within the data, a method which Mather frequently uses. Unfortunately, he fails to warn the reader that most statistically significant results of such heterogeneity tests will only be attributable to chance, and will prove nothing relative to the theories tested.

The second chapter on human genetics deals with tests of linkage in man. Mather finds the results obtained by Haldane (1936, *Ann. Eugen.* 7: 28–57) on the segregation of the retinitis pigmentosa locus and sex to have a very small probability on a theory of random assortment, and he states this to be unquestionable evidence for partial sex-linkage. However, the linkage is estimated as 43 $\pm$ 3 units, which is reasonably close to random assortment, demonstrating that the manner in which he applied the X^2 did not test solely for the presence of linkage. The remainder of this chapter deals with the u statistics and the problem of completeness of ascertainment, and with the detection of linkage without reference to parental phenotypes. These sections are well written, and it may be regretted that the chapter is completed by references to literature rather than by further exposition.

The last of the chapters on human genetics is on The Estimation of Gene Frequencies. It is useful, although incomplete. Recent works, particularly on blood groups, discuss this problem in greater detail.

Parts of the monograph are unsatisfactory. For example, for backcross data the maximum likelihood method is demonstrated at length, though it is briefly noted that the simpler method in current use gives identical results. On the other hand, the chapter on Symbols and Formulae recommends the simple technique by failing to list the maximum likelihood formula. The Symbols and Formulae chapter does not include a formula recommended in the book for testing backcross data when viability differences occur, and used to estimate the strength of the partial sex-linkage of retinitis pigmentosa. Notice is not taken of the fact that Haldane's more easily derived result differs from Mather's only by one part in three thousand. More counselling on the advantages of various methods seems warranted.

This edition differs from the first primarily by the addition of a section on Fisher's Scoring Method and the chapter on The Estimation of Gene Frequencies.

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Heredity in Uterine Cancer

By DOUGLAS P. MURPHY, Cambridge, Mass. Harvard University Press, Pp. 128, $2.50.

THIS book reports the results of a research project into the hereditary aspects, if any, of uterine cancer. It gives the details of the organization of the project for the benefit of those who might be considering conducting a similar study; the manner of acquiring the original patients with uterine cancer and of obtaining the control families for comparison; the sources of information; the manner of tabulating the data. This section actually comprises 35 pages, although as arranged in the book 24 pages are devoted to this; 26 pages are devoted to the appendices which furnish among other data, replicas of the actual questionnaires used in the study. The remaining 66 pages are taken up with the discussion of the results.

The results are presented in a series of 51 tables, some of which have more than one part. The tables are accompanied by a brief discussion of their contents. Many of the tables deal with the mechanism of obtaining information rather than with the actual results; such as "Sources of names and addresses of Probands"; "Cooperation of physicians"; "Success in securing history from potential probands"; "Informants who supplied data regarding relatives", etc. Incidentally, Murphy found that among the cancer patients' families only 54.2 per cent could give information on all the female relatives of 25 years of age and over, whereas in the control families, 73 per cent were able to furnish complete information on the corresponding group of female relatives. The author remarks "We can find no reason to explain this difference." The reviewer thinks there can be little doubt as to the explanation which is found in his Table 19a, which deals with the educational status of the probands. The percentages of those finishing only grade school were for the cancer probands 66.2%; for the controls 27.9; for those who completed high school the figures were 28.8 and 47.0 for the two groups; and for those who had a college education, 3.5% and 25.1% respectively. The higher the educational level, the more facilities there are in travel and correspondence for keeping in contact with one's relatives.

Murphy discussed the mother-daughter relationship in all families, cancer and control combined with respect to any form of cancer occurring in either one, and finds that only 9% of the mothers had cancer of some site when the daughters did not have any cancer, but that 17% of the mothers had cancer at some site if the daughter also had it. But the really essential point of the whole research which was "heredity of uterine cancer" not of cancer in general, is summed up in his finding that of the 18 mothers of the cancer probands who themselves had cancer, 6 or 33.3% had cancer of the uterus, while of the 26 mothers of the control cases who had cancer, only 2 or 8% had cancer of the uterus. The difference was statistically significant, ($P = 0.03$).

Inheritance of cancer of the breast is briefly discussed, Murphy stating "Since the cancer and the control family groups resembled each other to a very high degree in most respects, it was thought that an analysis of the occurrence of cancer of the breast in these two groups of families might be of some interest from the standpoint of its possible inheritance. . . . There was no unusual frequency of cancer of the breast in the cancer family groups, and no unusual concentration of cases of cancer of the breast in any one relationship." Murphy does not comment upon whether this finding is for or against a theory of inheritance of breast cancer, but conversations with readers of the book indicate that they consider the statement is offered as proof that there is no evidence for inheritance of cancer of the breast. Actually, if there is a genetic basis for inheritance of specific types of cancer, one would not expect to find a control population differing in incidence of breast cancer from a population of relatives of probands selected because they had *cervical* cancer.

Murphy concludes that hereditary factors affect the frequency with which cancer appears in the uterus. The proportion of cases of uterine cancer to all types of cancer was significantly higher in the cancer family groups (26%, or 36 cases out of 135) than in the control family groups (14.6%, or 26 cases out of 178). The comparable figures for mothers and aunts alone were 3.2% for cancer family groups as compared with 1.4% of control groups.

Murphy points out the unfortunate situation in which cancer of the cervix is not distinguished on many of the death certificates, (nor in fact in the minds of the persons reporting the family history) from cancer of the fundus of the uterus. This makes this type of study peculiarly difficult, since there seems to be no reason for assuming that cervical cancer and uterine fundus cancer are the same disease, with the same etiology. There also appear to be a number of excellent reasons for thinking that cervical and endometrial cancer are two separate entities. Thus the incidence of the two diseases differs (5 times or more as many cervical cancers as endometrial); the age distribution differs widely; (about 53% of cervical cancers are past 50, while 75% or more of endometrial cancers are past 50); the history of childbearing differs in the two (only 8% of cervical cancer cases have had no children while 28% of endometrial cancer cases have had none). All figures are taken from Ackerman and Regato. Should there be a marked difference in the role which heredity plays in determining cervical cancer on the one hand and endometrial carcinoma on the other, the inability to distinguish in the records which patients had one type, which the other, would tend to nullify any observations on the hereditary factors, if any, involved in either type. Not until these two types are clearly differentiated on death certificates, with pathological diagnoses accompanying each, will we be enabled to disentangle the two diseases. It may then be found that both exhibit the same degree of genetic control; but until that time, any statement as to the role of heredity in uterine cancer must remain suspect, since we cannot be certain that the same condition was under observation in all the persons said to have been suffering from uterine cancer.

A few points of criticism arise in connection with this study. One is that in the groups of relatives included in the tables 39, 44, 49, 50 which give the relationship of relatives in the cancer and control groups, the maternal and paternal uncles' wives are listed among the relatives. These cannot be included legitimately in the list of relatives since they are not related genetically to the probands. Although their exclusion does not affect the percentages given in the tables, their inclusion is not justified.

The second point is that volunteers who were accepted were screened as to the amount of cancer they had in their families. If they gave the slightest evidence that they were volunteering because there was "an unusual family history of cancer" they were refused. Several questions arise. What did the field worker who did the screening consider "an unusual family history of cancer"? In view of the fact that cancer is such a common cause of death, it would be unusual to have a family whose grandparents, parents, uncles, and aunts, cousins and sibs did not contain somewhere a few cancer deaths. How many cases of cancer among the relatives were necessary to exclude the volunteer? The next question in this connection follows: Were volunteers equally excluded if they volunteered because there was *no* cancer or an unusually *low* incidence of cancer among their relatives? If not, it would appear that the control group was selected in favor of there being a low incidence of cancer, which would prejudice the results.

The third point is of more serious import. Murphy states "The informant usually knew the cause of the relative's death. If the relative was certain of the cause, and it was not cancer, no further investigation was pursued". Having conducted a similar study in the field of breast cancer, I am only too aware of the fact that the "relative being certain" of the cause of death means nothing. If all the cancers which are capable of being uncovered in the family are found, (and this is still the minimal number since many were not diagnosed or recorded), it will be discovered that the patients and their relatives knew but a too small

part of them. Inasmuch as the fact that cancer is present is so often concealed not only from the patient but even from the immediate family, the persons interviewed give only a part of the cancers which can be proved to have existed. Thus in my own data, in which *every* cause of death was investigated, no matter how assured the informant was as to the cause of death, I find that only 51% of the cancers present in the parents were known to the informant; only 40% of the cancers present in their sibs were known, and only 28% of the cancers present in the aunts or uncles were reported. How many additional cases of cancer Murphy might have uncovered had every cause of death been investigated can only be guessed. The less educated the patient, the less reliable usually are the data which they supply as to causes of death. Since the cancer group was less well educated than the control group, Murphy probably missed out on a relatively greater proportion of cancer deaths among the cancer group than among the control. One can not remain confident that all cases are being reported by the patient or their relatives in their particular study until every statement is checked, and the reported incidence is compared with the observed incidence. It is unfortunate that this was not done.

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Understanding Heredity

By RICHARD B. GULDSCHMIDT, New York: J. Wiley and Sons, 1952. Pp. 228.

THIS book is an attempt by the author to present a survey of the basic facts of genetics at an elementary level. Written for the non-geneticist, the subject matter is presented with a minimum of technical language. The author has emphasized those parts of genetics essential for an understanding of the mechanism of heredity, and has purposely paid little attention to advances made in genetics during the more recent years. In general the book is easy to read and easy for a layman to understand. A few problems are given. A glossary is included.

The book opens with a chapter on hereditary and non-hereditary traits. This includes a discussion of the effects of heredity and environment in causing variation among genetically related individuals. Simple illustrations are used to exemplify the actions of hereditary and environmental factors causing similar phenotypes and to the results of selection and progeny tests in the two cases.

Most of the other chapters include subject matter found in any text on genetics, except that the author limited the number of phenomena discussed and used simpler and more easily understandable explanations. Topics discussed are: the physical basis for transmission of genes and chromosomes to body-cells, gametes, and progeny; hybridization and Mendel's laws of heredity with their universal application, including man; complete linkage, crossing over and mapping loci of genes on chromosomes; mutations of genes and chromosomes, a topic which is heard frequently in lay discussions and needs explaining; X and Y linkage and the relationship of those chromosomes to sex determination; multiple factors; and multiple alleles. The author uses the A B O blood groups in man as an example of multiple alleles; the Rh grouping is mentioned but not discussed fully.

In order that the reader may become interested in more advanced phases of genetics, the author has introduced some of the topics in the last chapter. These include cytogenetics, genetics of microorganisms, cytoplasmic inheritance, physiological and biochemical genetics, and genetics in evolution.

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General Genetics

By A. M. Srb (Cornell University) and R. D. Owen (California Institute of Technology) San Francisco: W. H. Freeman and Co., 1952. Pp. 561; 182 illus., 62 tables. $5.50.

Hematologists are confronted more and more with the need for a thorough understanding of the fundamental principles of heredity. There are many hematological disorders for which a knowledge of genetics is essential, for example, hemophilia, hereditary spherocytosis, sickle cell anemia, Mediterranean anemia, and especially erythroblastosis fetalis. Therefore, there is need for an authoritative elementary but comprehensive book on general genetics which hematologists and other research workers can consult for information regarding the basic principles of genetics and their applications. The excellent book by Srb and Owen fills this need admirably.

The attractive features of Srb and Owen's book are the freshness and modernity of its approach and the repeated references to human genetics. The bibliography at the end of each chapter listing reviews and articles on which the material presented is based demonstrate how up-to-date the volume is, because most of these references are less than five years old. The text is amplified by sections on questions and problems at the end of each chapter, where the reader is presented with additional observations on plants, lower animals, and man, and required to work out the genetic mechanism. This is a valuable feature of the book, because one of the characteristics of the science of genetics is that the number of fundamental principles involved is relatively small; while the diversity of the applications of these principles is great. The reader soon learns how to recognize the principles that are involved no matter how much they may disguised by the peculiar character of the observations.

The book is intended primarily as a text for elementary courses in genetics, and for this purpose it is eminently suited and will certainly be widely adopted by colleges throughout the country. It is also a book that physicians should acquire, to read with interest and profit. The elementary principles of genetics are clearly presented with the aid of some relatively recent interesting observations from animal and plant genetics. Moreover, applications to human genetics are pointed out, and among the first problems the reader is required to work out for himself are the heredity of thalassemia and Pelger's anomaly. Mendel's pioneering work is of course suitably recognized, and his observations are deftly presented as problems at the end of the chapters dealing with elementary principles.

In the earlier chapters, the reader is confronted with the problem of mechanism of gene action, a fundamental question with which modern genetics is largely concerned. In contrast to earlier books on genetics, this new volume attempts to budge the mystic gap between genotype and phenotype, and points out that this problem is largely if not entirely a biochemical one. Examples from animal and plant genetics show that the gene frequently determines the production of a particular enzyme which reacting on a special substate, either derived from the environment or conditioned by other genes, gives rise to the observed phenotype. It is also pointed out early in the book how the expression of a gene may be modified or even suppressed by the impact of the environment, both external and internal. Thus, as the author pointed out the controversy regarding the relative importance of heredity and environment (nature is nurture) is largely pointless.

Additional chapters deal with sex determination and sex linkage (including a discussion of the heredity of hemophilia), the chromosomes, life cycles, linkage and chomosome mapping, chromosome aberrations, mutations, quantitative inheritance, imbreeding and selection,

genes and cellular biochemistry and development, the nature of the gene, evolution, and practical applications in animal and plant breeding and eugenics.

The excellent quality of the volume may perhaps best be illustrated by the sections on human blood grouping and erythroblastosis fetalis. These difficult problems are so clearly explained that the reader with no prior knowledge of the subject can grasp it without difficulty.

The clear text is amplified by excellent diagrams, and one of the admirable feature of the book is the liberal use of original informative diagrams and line drawings to round out and further explain the text materials. Another remarkable feature of the book is that while it is written primarily for the neophyte, it is so comprehensive and up-to-date that it can be read with enjoyment also by individuals already familiar with genetics. The section on Rh-Hr genetics has been particularly well done—indeed the book is unique since it is one of the few reviews that reveals insight into the true nature of the difference between the viewpoints of Rh-Hr and C-D-E workers. This section by itself makes the book required reading for hematologists, especially those working on the Rh blood types and erythroblastosis fetalis.

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The Board of Directors
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BIBLIOGRAPHY OF HUMAN GENETICS

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This section is a continued list of references to recent and current articles and books which may be of interest to students of Human Genetics. An attempt has been made, and is being made, to make the list complete, but to do so is a difficult task. Everyone who finds the list useful and considers a complete one desirable, can be of help by sending to the bibliographic editor, at the address given above, any recent reference which has been missed or any current reference which it seems probable may be missed as a result of its appearance in a journal which probably is not systematically covered by the bibliographic editor. If a reference to an article is sent in be sure that it is complete with respect to name of author(s), year of publication, title of article, name of journal, volume number, and first and last page numbers. If the reference is to a book be sure that it includes name of author(s), year of publication, title, name of publisher, place of publication, and number of pages. Whenever possible send the mailing address of the author (senior author only if more than one) of the article or book.

ALLAN, T. M. 1952. Blood-groups and reproduction. *Lancet*, Lond. 1(2): 102–103.

ALLAN, T. M. 1952. Blood-groups and reproduction. *Lancet*, Lond. 1(7): 370–371.

ALSTRÖM, C. H. 1950. A study of epilepsy in its clinical, social, and genetic aspects. *Acta psychiat. neur.*, Kbl. Suppl. No. 63. 284 p.

ANONYMOUS. 1951. Finger-printing the blood. *S. Afr. M. J.* 25(41): 740–741.

ANONYMOUS. 1951. What is Mongolian about Mongolism? *S. Afr. M. J.* 25(42): 761.

ANONYMOUS. 1951. What is Mongolian about the Mongolian spot? *S. Afr. M. J.* 25(43): 777.

ANONYMOUS. 1952. Blood-groups in disputed paternity. *Lancet*, Lond. 1(6): 296–297.

ARMATTOE, R. E. G. 1951. ABO and Rh blood types among the ewes of West Africa. *Am. J. Phys. Anthrop.* 9(3): 371–373.

ASCHNER, B. M., HURST, L. A., & ROIZIN, L. 1952. A genetic study of Paget's disease (osteitis deformans) in monozygotic twin brothers. *Acta genet. med. gemellol.*, Roma 1(1): 67–79.

AUXILIA, F. 1951. Indagine statistica sul destino della prole di madre minorate psichiche. [A statistical study of the fate of the progeny of mentally defective mothers.] *Minerva pediat.* 3(1): 9.

AYE, C. 1951. Carie dentaire et génétique. [Dental caries and genetics.] *Med. & hyg.*, Geneva 9(204): 387–398.

BAFFI V., & AURICCHIO, G. 1951. Considerazioni sulla patogenesi dell'idiozia amaurotica familiare; a proposito di un caso di forma infantile mallattia di Tay-Sachs. [Pathogenesis of familial amaurotic idiocy; infantile form of Tay-Sachs disease.] *Pediatria*, Nap. 59(7–8): 527–539.

BAILEY, N. T. J. 1951. A classification of methods of ascertainment and analysis in estimating the frequencies of recessives in man. *Ann. Eugen.*, Lond. 16(3): 223–225.

BAILEY, N. T. J. 1951. The estimation of the frequencies of recessives with incomplete multiple selection. *Ann. Eugen.*, Lond. 16(3): 215–222.

BARNICOT, N. A., HARRIS, H., & KALMUS, H. 1951. Taste thresholds of further eighteen compounds and their correlation with P. T. C. thresholds. *Ann. Eugen.*, Lond. 16(2): 119–128.

BAUMANN, T. 1951. Konstitutionelle Panmyelophthise mit multiplen Abartungen; (Fanconi-Syndrom). [Constitutional panmyelophthisis with multiple anomalies (Fanconi syndrome).] *Ann. paediat.*, Basel 177(3): 142–174.

BENCINI, M. A. 1952. Contributo clinico allo studio del mongolisme nei gemelli; presentazione di una coppia di gemelle monozigotiche. [Clinical contribution to the study of mongolism in twins; presentation of a pair of monozygotic twins.] *Acta genet. med. gemellol.*, Roma 1(1): 29–39.

BENSBERG, G. J. 1952. Performance of brain-injured and familial mental defectives on Bender Gestalt test. *J. Consult. Psychol.* 16(1): 61–64.

BERNSTEIN, M. E. 1952. Studies in the human sex ratio. II. The proportion of unisexual sibships. *Human Biol.* 24(1): 33–43.

BERTINCHAMPS, A. J. 1951. Le mongolisme. *Bruxelles mêd.* 31(42): 2188–2198.

BINETTI, P. 1951. Il fattore "ereditarietà" nella malinconia involutiva. [The hereditary factor of involutional melancholia.] *Gior. psichiat.* 79(2): 169–188.

BJELKHAGEN, I. 1950. A case of infantile amaurotic family idiocy. *Acta paediat.*, Upps. 39(4–5): 445–451.

BLAND, E. F., FIELD, R. A., FIREDLICH, A., & EYLER, W. R. 1951. Clinico-pathological conference; familial idiopathic hypertrophy of the heart. *Am. Practitioner* 2(10): 890–894.

BONNIER, G. 1952. Indirect effects of x-rays on chromosomes. *Brit. J. Radiol.* 25(292): 180–182.

BONOMINI, B., & GREGORIS, L. 1951. Nuovo tipo di osteopetrosi generatizzata famigliare. [New type of generalized familial osteopetrosis.] *Acta med. patav.* 12(9): 373–394.

BÖÖK, J. A. 1951. Arftlighet och risksiffror inom pediatriken. [Heredity and risk figures in pediatrics.] *Nord. med.* 46(41): 1513–1516.

BÖÖK, J. A. 1951. The incidence of congenital diseases and defects in a south Swedish population. *Acta genet.*, Basel 2(4): 289–311.

BOYD, W. C. 1952. Newer concepts of human races suggested by blood group studies. *J. Nat. M. Ass.* 44(1): 1–6.

BREWER, J. I., JONES, H. O., & CULVER, H. 1952. True hermaphroditism. *J. Am. M. Ass.* 148(6): 431–435.

BUSSI, L., & FRANZINI, P. 1951. Contributo allo studio ematologico ed anatomo-isologico dell'anemia microcitica constituzionale. [Hematologic and anatomo-histologic study of constitutional microcytic anemia.] *Gior. clin. med.* 32(12): 1360–1371.

CALZOLARI, G. 1951. Rilievi clinico-statistici gravidanza gemellare; casistica del decennio 1940–1949 della Scuola Ostetrica di Ferrara. [Clinical and statistical data on twin pregnancies from 1940–1949 at the Scuola Ostetrica di Ferrara.] *Arcisped. S. Anna di Ferrara* 4(3): 300–310.

COLE, W. R., & LEVIN, S. 1951. Cleidocranial dysostosis. *Brit. J. Radiol.* 24(286): 549–555.

CONTI, C., & NELLO, R. P. 1950. Il disordine genetico del ricambio colesteridico nella colelitiasi. [Genetic disorders of cholesterol metabolism in cholelithiasis.] *Rass. fisiopat.* 22(10): 1003–1056.

CRECELIUS, W. 1952. Ein Beitrag zum Krankheitsbild der Osteopathia dysplastica familiaris. [Aspects of familial dysplastic osteopathy.] *Fortsch. Röntgenstrahl.* 76(2): 196–202.

CRIGLER, J. F., & NAJJAR, V. A. 1952. Congenital familial nonhemolytic jaundice with kernicterus: a new clinical entity. *A. M. A. Am. J. Dis. Child.* 83(2): 259–260.

CUNNINGHAM, G. C., & KELLY, J. J. 1952. Pyloric stenosis in monovular twins; report of a case. *South. M. J.* 45(1): 75–76.

DAHLBERG, G. 1952. Die Tendenz zu Zwillingsgeburten. [Tendency for twin births.] *Acta genet. med. gemellol.*, Roma 1(1): 80–88.

DOLL, R., & KELLOCK, T. D. 1951. The separate inheritance of gastric and duodenal ulcers. *Ann. Eugen.*, Lond. 16(3): 231–240.

DOMINGUEZ NAVARRO, L. 1951. Fragilidad ósea esencial y exostosis osteogénica. [Fragilitas ossium and exostosis.] *Med. & cir. guerra*, Madr. 13(3–4): 73–85.

DREYFUSS, F., MUNDEL, G., & BENYESCH, M. 1951. Sickle cell disease among Yemenite Jews. [In Hebrew with English summary.] *Harefuah*, Tel-Aviv 41(9): 167–171.

DUBLIN, W. B. 1951. Neurologic lesions of erythroblastosis fetalis in relation to nuclear deafness. *Am. J. Clin. Path.* 21(10): 935–939.

ELSHOVE, P. 1951. Vier gevallen van aangeboren hartgebrek in één familie. [Four cases of congenital heart defect in one family.] *Ned. tschr. geneesk.* 95(38): 2768–2771.

FAIRWEATHER, D. S. 1950. Mental deficiency. In FLEMING, G. W. T. H., *Recent Progress in Psychiatry* 2: 510–550. 2nd ed. London: Churchill.

FALLS, H. F. 1951. The role of heredity in ophthalmology. *N. Y. State J. M.* 51(22): 2624–2627.

FASSBINDER, W. 1951. Eine seltene Doppelmissbildung. [Rare instance of double monster.] *Beburtsh. & Frauenk.* 11(9): 837–844.

FLYNN, J. T., KENNEDY, M. A. K., & WOLF, S. 1949. Essential hypertension in one of identical twins; an experimental study of cardiovascular reactions in the Y twins. *Res. Pub. Ass. Nerv. Ment. Dis.* 29: 954–961.

FORNI, S. 1951. Diagnostic et symptomatologie de la dégénérescence cristalline héréditaire de la cornée; ses rapports avec les affections cornéennes caractérisées par des dépôts de cristaux. [Diagnosis and symptomatology of hereditary crystalline degeneration of the cornea; relation to corneal diseases characterized by crystal deposits.] *Arch. opht.*, Par. 11(6): 541–563.

FORSYTH, C. C., & UCHIDA, I. 1951. Auricular septal defect in one of monozygotic twins. *Arch. Dis. Childh.*, Lond. 26(130): 582–587.

FRANCESCHETTI, A., & KLEIN, D. 1952. Oxycephalie chez trois paires de jumeaux univitellins, associée dans un des cas á une cutis frontis gyrata. [Oxycephaly in three pairs of monozygotic twins, associated in one case with cutis frontis gyrata.] *Acta genet. med. gemellol.*, Roma 1(1): 48–66.

FRANQUELO RAMOS, E. 1951. Ulcera duodenal en hermanos gemelos univitelinos. [Duodenal ulcer in enzygotic twin brothers.] *Rev. clín. españ.* 42(1): 44–46.

FRUMIN, A. M., & KOHN, A. 1951. Acquired hemolytic anemia of the newborn (erythroblastosis foetalis) due to O–B isoimmunization; report of case. *Arch. Pediat.* 68(10): 461–466.

FRY, J. 1952. Familial erythema nodosum. *Brit. M. J.* 1(4757): 529–531.

GAIN, D. D., & LAWSON, D. E. 1952. Osteogenesis imperfecta. *Radiology* 58(2): 221–223.

GARN, S. M. 1951. The use of middle-phalangeal hair in population studies. *Am. J. Phys. Anthrop.* 9(3): 325–333.

GEDDA, L. 1952. Genetica, medicini e costituzione. [Genetics, medicine and constitution.] *Acta genet. med. gemellol.*, Roma 1(1): 1–7.

GILBERTO BELTRAMINO, A. 1950. Fecundación artificial y eugenesia. [Artificial insemination and eugenics.] *An. med. púb.*, Santa Fe 2(3–4): 611–614.

GILLIES, H. 1950. Schizophrenia. In FLEMING, G. W. T. H., *Recent Progress in Psychiatry* 2: 346–378. 2nd ed. London: Churchill.

GORDON, A. 1951. Epilepsy as a mental hygiene problem. *Int. Rec. Med.* 164: 465–468.

GORDON, W. H., KAUFMAN, J. M., & KASHTON, H. A. 1952. Myotonica congenita; report of four cases in one family; one with autopsy findings. *J. Michigan M. Soc.* 51(2): 188–194.

GREBE, H. 1951. Kann Chondrodysplasie erworken sein? [Heredity of chondrodysplasia.] *Zbl. Gyn.* 73(19): 1552–1558.

GREBE, H. 1952. Diskordanzursachen bei erbgleichen Zwillingen. [Major differences in monozygotic twins.] *Acta genet. med. gemellol.*, Roma 1(1): 89–102.

GROVE-RASMUSSEN, M., LOGHEM, J. J. VAN, & MAGNEE, W. 1951. The rare gene CdE (r_y) in a Basque family. *Ann. Eugen.*, Lond. 16(2): 131–133.

GUREVITCH, J. 1951. Incompatibility in the blood group systems Rh–Hr, ABO. [In Hebrew with English Summary.] *Harefuah,* Tel-Aviv 41(8): 141–144.

GUREVITCH, J., HERMONI, D., & POLISHUK, Z. 1951. Rh blood types in Jerusalem Jews. *Ann. Eugen.*, Lond. 16(2): 129–130.

HALLGREN, B. Specific dyslexia (congenital word-blindness); a clinical and genetic study. *Acta psychiat. neur.*, Kbh. Suppl. No. 65.

HANHART, E. 1951. L'importance de la constitution organique et de l'hérédité pour les manifestations les maladies allergiques. [Importance of organic constitution and heredity in manifestations of allergic diseases.] *Med. & Hyg.*, Geneva 9(205): 405.

HARRIS, H., & KALMUS, H. 1951. The distribution of taste thresholds for phenylthiourea of 384 sib pairs. *Ann. Eugen.*, Lond. 16(3): 226–230.

HARRIS, H., & MCARTHUR, N. 1951. Changes in sex incidence of diabetes mellitus, (1912–1947). *Ann. Eugen.*, Lond. 16(2): 109–118.

HENRY, J. 1951. Family structure and the transmission of neurotic behavior. *Am. J. Orthopsychiat.* 21(4): 800–818.

HETZEL, P. S. 1951. Idiopathic hyperlipaemia with a report of two cases occurring in one family, and a review of the literature. *Med. J. Austral.* 2(12): 396–399.

HILLMAN, J. W., & JOHNSON, J. T. H. 1952. Arthrogryposis multiplex congenita in twins. *J. Bone Surg.* Am. Vol. 34-A(1): 211–214.

HOLLÄNDER, L. 1951. Der derzeitige Stand der Blutgruppenforschung (Übersiehlsreferat). [Present state of research on blood groups.] *Acta haemat.*, Basel 6(6): 377–383.

HOLLÄNDER, L. 1951. Über die Blutgruppe Duffy und ihre Verteilung in Basel. [Duffy blood grouping and its distribution in Basel.] *Acta haemat.*, Basel 6(5): 257–261.

HOLMGREN, S. 1950. Congenital deaf-mutism in a family with dystrophia reticularis laminae pigmentosae retinae (Sjogren). *Acta ophth.*, Kbh. 28(3): 279–300.

HOLZEL, A., & SHER, N. 1952. Familial jaundice of the newborn associated with hepatosteatosis. *Arch. Dis. Childh.*, Lond. 27(131): 37–42.

HOWARD, A. 1952. Radiation genetics: I. Genetic aspects of radiation risks. *Brit. J. Radiol.* 25(292): 177–179.

HURST, L. A. 1952. Electroencephalographic support for a genetically oriented organic concept of schizophrenia. *J. Nerv. Ment. Dis.* 115(2): 95–120.

INGHAM, W. N. 1952. A familial crisis in congenital acholuric jaundice. *Arch. Dis. Childh.*, Lond. 27(131): 34–36.

JACKSON, A. D. M., & LAWLER, S. D. 1951. Pachyonchia congenita; a report of six cases in one family, with a note on linkage data. *Ann. Eugen.*, Lond. 16(2): 142–146.

JACKSON, W. P. U. 1951. The clinical features, diagnosis, and osseous lesions of gargoylism exemplified in three siblings. *Arch. Dis. Childh.*, Lond. 26(130): 549–557.

JAMES, T. 1951. Aplasia of the male prepuce with evidence of hereditary transmission. *J. Anat.*, Lond. 35(4): 370–372.

JERSILD, T., & PERDRUP, A. 1950. Familial occurrence of necrosis adiposa neonatorum. *Acta paediat.*, Upps. 39(4–5): 389–394.

KALLMAN, F. J. 1951. Recent progress in relation to the genetic aspects of mental deficiency. *Am. J. Ment. Defic.* 56(2): 375–381.

KANOF, A. 1952. Ehlers–Danlos syndrome; report of a case with suggestion of a possible causal mechanism. *A. M. A. Am. J. Dis. Child.* 83(2): 197–202.

KAPLAN, E., ZUELZER, W. W., & NEEL, J. V. 1951. A new inherited abnormality of hemoglobin and its interaction with sickle cell hemoglobin. *Blood* 6(12): 1240–1249.

KAPLAN, E., ZUELZER, W. W., & NEEL, J. V. 1952. Studies concerning a new inherited abnormality of hemoglobin. *A. M. A. Am. J. Dis. Child.* 83(2): 258–259.

KING, E. L., & KING, J. A. 1951. Experience with the Rh factor in 1000 consecutive white obstetrical patients. *Am. J. Obst.* 62(4): 758–763.

KLIJNHOUT, A. 1949–1950. Szondi-test und Heredität. [The Szondi test and heredity.] *Criança portug.* 9: 367–405.

KLOTZ, H. P. 1951. Le bon gène du bon père de famille (l'eu-gène). [Eugenics and better families.] *Médecin fr.* 11(10): 196.

KOSTLAN, J., & STRAKOVA, M. 1951. Vývoj zubů při osteogenesis imperfecta. [Development of teeth in osteogenesis imperfecta.] *Česk. stomat.* 51(10): 407–420.

KULENKAMPFF. 1951. Uber das Rhinophym und seine behandlung; ein Beitrag zur Genpathologie. [Rhinophyma and its treatment; a contribution to genic pathology.] *Derm. Wschr.* 124(41): 1012–1013.

KURAHASHI, M. 1950. The family investigation of the pseudologist. [In Japanese with English summary.] *Jap. J. Psychol.* 20(4): 23–25.

LAWSON, D. 1951. The incidence of pyloric stenosis in Dundee. *Arch. Dis. Childh.*, Lond. 26(130): 616–617.

LEVINE, P., KUHMICHEL, A. B., WIGOD, M., & KOCH, E. 1951. A new blood factor, s, allelic to S. *Proc. Soc. Exp. Biol.*, N. Y. 78(1): 218–220.

LEVINE, P., KUHMICHEL, A. B., & WIGOD, M. 1952. A second example of anti-Cellano (anti K). *Blood* 7(2): 251–254.

LEVITT, J. M., & LLOYD, R. I. 1952. Congenital and familial endothelial defects. *Am. J. Ophth.* 35(3): 342–349.

LODBERG, C. V., & LUND, A. 1950. Hereditary optic atrophy with dominant transmission; three Danish families. *Acta ophth.*, Kbh. 28(4): 437–468.

LUNDIN, G., & MÖLLER, A. 1951. Views on the question of sterilization of epileptics. *Acta psychiat. neur. scand.* 26(2): 177–189.

MCCORMACK, C. J., & KEARNEY, M. W. 1952. Is duodenal ulcer hereditary? *Connecticut M. J.* 16(2): 82–85.

MCKEOWN, N. T., MACMAHON, B., & RECORD, R. G. 1951. The familial incidence of congenital pyloric stenosis. *Ann. Eugen.*, Lond. 16(3): 260–281.

MARTIN, C. A., & NADEAU, G. 1951. L'oligophrenie phenylpyruvique. *Laval méd.* 16(9): 1166–1178.

MARTINEZ APARICIO, A. 1951. Bloqueo incompleto de rama izquierda familiar. [Familial incomplete left bundle branch block.] *Rev. cubana cardiol.* 12(1): 15–18.

MASSOTTI LITTEL, A. L. 1951. Dos casos de luxación habitual del hombro en el niño de carácter congenito y familiar. [Two cases of habitual dislocation of the shoulder of congenital and familial character in children.] *Rev. clin. espan.* 42(3): 190–196.

MAYR, E. 1951. Die klinische Bedeutung des Rh Blutfaktoren-Systems. [Clinical significance of Rh blood groups.] *Med. Klin.*, Berl. 46(38): 1001–1004.

METSON, B. F., & WILLIAMS, B. K. 1952. Hereditary ectodermal dysplasia of the anhidrotic type; report of a case in a Negro. *J. Pediat.*, S. Louis 40(3): 303–309.

MOHR, J. 1951. Taste sensitivity to phenylthiourea in Denmark. *Ann. Eugen.*, Lond. 16(3): 282–286.

MOSBECH, J. 1951. Congenital malformation of the nails associated with deformities of the elbows and knees (monozygotic twins). *Acta genet.*, Basel 2(4): 312–317.

MÜLLER, F. 1951. Ein Stammbaum von hereditärer Optikusatrophie (Leber). [A genealogy of Leber's hereditary atrophy of the optic nerve.] *Klin. Mbl. Augenh.* 119(1): 62–76.

MURANO, G. 1951. Contributo alla conoscenza della predisposizione allergica eredofamiliare nel favismo. [Heredofamilial allergic predisposition in favism.] *Pediatria*, Nap. 59(7–8): 479–517.

NEEL, J. V., & FALLS, H. F. 1951. The rate of mutation of the gene responsible for retinoblastoma in man. *Science* 114(2964): 419–422.

NEEL, J. V., WELLS, I. C., & ITANO, H. A. 1951. Familial differences in the proportion of abnormal hemoglobin present in the sickle cell trait. *J. Clin. Invest.* 30(10): 1120–1124.

NIETO, D. 1950. La herencia en las enfermedades nerviosas y mentales; metodologiá y resultados. [Heredity in nervous and mental diseases; methodology and results.] *Rev. mex. Psiquiat. Neurol., Neurocirug.* 1(1): 1–7.

NIEUWENHUIZSE, A. C. 1950. Continuation of the pedigree of hereditary potato nose (benjamins-stibbe). *Acta otolar.*, Stockh. 38(2): 112–119.

NOOJIN, R. O., REYNOLDS, J. P., & CROOM, W. C. 1952. Genetic study of hereditary type of epidermolysis bullosa simplex. *A. M. A. Arch. Derm. Syph.* 65(4): 477–483.

NUNES, S. 1949–1950. Incompatibilidade sanguínea nas neuro-psicopatias infantis. [Blood incompatibility in neuropsychopathic children.] *Criança portug.* 9: 309–320.

OLÉRON, P. 1950. Psychologie differentielle. *Bull. Groupe Etudes Psychol.*, Univ. Paris 3(4): 58–66; (5–6): 38–39; (7): 42–45; (8) 40–41; (9) 35–37; (11): 41–44; (12): 66–67; (13): 14–17.

OLIVER, C. P. 1950. Mongolism: multiple occurrence in sibships. *Eugen. News* 35: 35–39.

PECORELLA, F., & PULEJO, S. 1951. Un nuovo caso di trombocitopatia costituzionale ereditaria tipo willebrand-jurgens. [New case of hereditary constitutional thrombocytopathy, Willebrand-Jürgens type.] *Pediatria*, Nap. 59(7–8): 549–564.

PENROSE, L. S. 1951. Data for the study of linkage in man; phenylketonuria and the ABO and MN loci. *Ann. Eugen.*, Lond. 16(3): 241–248.

PENROSE, L. S. 1951. Maternal age in familial mongolism. *J. Ment. Sc.*, Lond. 97(409): 738–747.

PENROSE, L. S. 1951. Measurement of pleiotropic effects in phenylketonuria. *Ann. Eugen.*, Lond. 16(2): 134–141.

PFEIFFER, J. 1950. Genetics—the science of heredity. *Publ. Affairs Pamphl.* No. 165.

PORTIER, A., CABANNES, R., MASSONNAT, J., & ZEVACO, P. 1951. Les syndromes hématologiques méditerranéens (thalassemia) chez l'indigene musulman algérein. [Mediterranean hematological syndromes (thalassemia) in Mohammedan natives of Algeria.] *Ann. méd.*, Par. 52(6): 608–644.

PROVENZANO, R. W. 1951. Congenital hemolytic disease due to ABO incompatibility. *Connecticut M. J.* 15(6): 476–478.

REESE, A. J. M., & LEVY, E. 1951. Familial incidence of non-lipoid reticuloendotheliosis (Letterer-Siwe disease). *Arch. Dis. Childh.*, Lond. 26(130): 578–581.

RIFE, D. C. 1950. Heredity and the eyes. *O–eye–O* 16(3): 10–17.

RIFE, D. C. 1952. Twins and research. *Acta genet. med. gemellol.*, Roma 1(1): 14–23.

ROGERS, J. D., & BICKEL, W. H. 1952. An unusual form of osteo–arthropathy present bilaterally in the knees of two brothers. *J. Bone Surg.* Am. Vol. 34–A(1): 135–143.

SAGGESE, M., & CROCCO, G. 1951. Su due casi anemia di Jaksch-Hayem-Luzet in due coppie di gemelli. [Two cases of Jaksch–Hayem–Luzet anemia in two sets of twins.] *Pediatria*, Nap. 59(7–8): 565–576.

SALA SANCHEZ, T. 1951. Sobre un caso de osteogénesis imperfecta precoz (tipo Vrolik) asociado a otras malformaciones. [Case of osteogenesis imperfecta praecox (Vrolik) associated with other malformations.] *Acta pediat. espan.* 9(108): 1403–1422.

SCHINDLER, J. A., & KINDSCHI, L. G. 1951. Juvenile cirrhosis of the liver in three members of the same family. *Wisconsin M. J.* 50(10): 1004–1008.

SCHEINFELD, A. 1950. *The New You and Heredity.* Philadelphia: Lippincott. 616 p.

SCHMËING, K. 1950. *Der Sinn der Reifungsstufen, Erbgang und Werdegang der menschlichen Jugend.* [The meaning of maturational stages: hereditary and developmental processes in human youth.] 3rd ed. Leipzig: Johann Ambrosius Barth. 110 p.

SCHULZ, B. 1951. Auszählungen in der Verwandtschaft von nach Erkrankungsalter und Geschlecht Gruppierten Manisch-Depressiven. [A statistical analysis of mental disorders in the families of manic–depressives grouped by age and sex.] *Arch. Psychiat.* Berl. 186(6): 560–576.

SCHWARTZ, S. O., FITZPATRICK, W. J., & MASON, J. 1952. Incidence of sickle cell disease. *Acta haemat.*, Basel 7(1): 43–46.

SCHWESINGER, G. C. 1952. The effect of differential parent–child relation of identical twin resemblance in personality. *Acta genet. med. gemellol.*, Roma 1(1): 40–47.

SEITZ, A., & BAUTZE, H. J. 1951. Familiärer Anus vestibularis. [Familial anus vestibularis.] *Zbl. gyn.* 73(19): 1543–1545.

SHELDON, W. H., & BALL, R. 1949. Physical characteristics of the Y twins and their relation to hypertension. *Res. Pub. Ass. Nerv. Ment. Dis.* 29: 962–975.

SINGER, K., & CHERNOFF, A. I. 1952. Studies on abnormal hemoglobins. III. The interrelationship of type S (sickle cell) hemoglobin and type F (alkali resistant) hemoglobin in sickle cell anemia. *Blood* 7(1): 47–52.

SLATER, E. 1950. Psychiatric genetics. In FLEMING, G. W. T. H., *Recent Progesss in Psychiatry* 2: 1–25. 2nd ed. London: Churchill.

SLATER, E. 1950. The genetical aspects of personality and neurosis. *Congrès International de Psychiatrie, Paris, Rapports* 6: 119–154.

SMYTH, C. J. 1951. The genetic aspects of rheumatic disease. *Bull. Rheum. Dis.* 2(4): 7–8.

SORENSEN, H. R. 1951. Familiaer optraeden af congenite hjertelidelser. (Familial occurrence of congenital heart lesions.] *Nord. med.* 46(38): 1402–1403.

STEVENS, W. L. 1952. Statistical analysis of the A–B–O system in mixed populations. *Human Biol.* 24(1): 12–24.

STOCKS, P. 1952. Recent statistics of multiple births in England and Wales. *Acta genet. med. gemellol.*, Roma 1(1): 8–13.

STOHLMAN, F. JR., HARRINGTON, W. J., & MOLONEY, W. C. 1951. Parahemophilia (Owren's disease); report of a case in a woman with studies on other members of her family. *J. Laborat. Clin. M.* 38(6): 842–845.

STRANDSKOV, H. H., & WASHBURN, S. L. 1951. Genetics and physical anthropology. *Am. J. Phys. Anthrop.* 9(3): 261–263.

STREIFF, E. B., & PORTMANN, U. P. 1951. Betrachtungen über die Entwicklung und die Vererbung gefässähnlicher Netzhautstreifen. [On the development and heredity of angioid streaks of the retina.] *Klin. Mbl. Augenk.* 119(1): 88–89.

STRUTHERS, D. 1951. ABO groups of infants and children dying in the west of Scotland (1949–1951). *Brit. J. Social M.* 5(4): 223–228.

STURGEON, P., ITANO, H. A., & VALENTINE, W. N. 1952. Chronic hemolytic anemia associated with thalassemia and sickling traits. Blood 7(3): 350–357.

SUN, S. F. 1951. Heredodegeneration of the macula lutea, with a report of a case of infantile type without cerebral symptom. *Chin. M. J.* 69(9–10): 440–444.

ŠVÁB, V., & BEK, V. 1951. Dědičná osteopoikilie ve třech generacích. [Hereditary osteopoikilosis in three generations.] *Čas. lék. česk.* 90(51–52): 1518–1521.

TOGERSEN, J. 1951. Hereditary and environmental factors in twinning. *Am. J. Phys. Anthrop.* 9(4): 441–454.

TONNING, H. O., WARREN, R. F., & BARRIE, H. J. 1952. Familial haemangiomata of the cerebellum; report of three cases in a family of four. *J. Neurosurg.* 9(2): 124–132.

TOURAINE, A. 1951. Publier des observations de génétique medicale. [More publications of medical genetics observations are needed.] *Presse méd.*, Par. 59(63): 1301–1302.

TREVOR-ROPER, P. D. 1952. Marriage of two complete albinos with normally pigmented offspring. *Brit. J. Ophth.* 36(2): 107–108.

VAN LINT, A. 1951. A propos du déterminisme du sexe. [On sex determination.] *Bruxelles méd.* 31(44): 2300–2302.

VENABLE, H. P. 1952. Glaucoma in the Negro. *J. Nat. M. Ass.* 44(1): 7–14.

VEYT, F. DE, & MOIA, V. 1951. Le syndrome de Turner et ses relations avec le status Bonnevie–Ullrich. [Turner syndrome and its relation to status Bonnevie–Ullrich.] *Ann. endocr.*, Par. 12(6): 1111–1118.

VULPIAN, P. DE, KIRSCH, J., & LEVREL, P. 1951. Une ostéopoecilie familiale. [Familial osteopecilia.] *J. radiol. électr.* 32(5–6): 465–469.

WASSERMAN, C. F., PHELPS, V. R., & HERTZOG, A. J. 1952. Chronic hemolytic anemia in a white child due to thalassemia and sicklemia; with a genealogic survey. *Pediatrics* 9(3): 286–289.

WATSON, E. M., & THOMPSON, M. W. 1951. Heredity and diabetes. *Am. J. Digest. Dis.* 18(11): 326–330.

WEINER, R. 1951. Heredity and the x-ray technician. *X-ray Technician* 23(3): 186–188.

WHEELAN, L. 1951. Aggressive psychopathy in one of a pair of uniovular twins; a clinical and experimental study. *Brit. J. Delinquency* 2: 130–143.

WILSON, D. C. 1951. Families of manic depressives. *Dis. Nerv. Syst.* 12(12): 362–369.

WOLFF, J. A., & VON HOFE, F. H. 1951. Familial erythroid multinuclearity. *Blood* 6(12): 1274–1283.

WORSTER-DROUGHT, C. 1952. Four cases of poliomyelitis in the same family. *Lancet*, Lond. 1(2): 103.

ZABERDINOS, A. 1952. Sickle cell anemia in a white adult. *J. Am. M. Ass.* 148(7): 549–550.

Report of the Secretary

A. Membership and Subscribers to the Journal

The membership of the Society and subscribers as of September 2, 1952 was as follows:

Active members	424
Associate members	7
Corresponding members	39
Individual, non-member subscriptions	19
Institutional subscriptions	
Foreign	59
Domestic	180
GRAND TOTAL	728

The seven associate members do not receive the Journal which leaves a total of 721. This is only 84 more subscriptions than the 637 reported by Dr. Strandskov last year. Actually, 168 new subscriptions were obtained which means that we lost 84 members who were two or more years in arrears, who resigned, or died. There are 118 members or institutions in arrears for their 1952 dues. Every effort will be made by the treasurer to collect these.

The secretary wishes to thank every member, most heartily, for the vigorous response and successful action in the membership drive. The results were most gratifying; but we are far from solvency, as yet, without the aid of outside grants. We must make a *net* gain of more than 200 members in order to "break-even" on Journal costs. This means almost 300 new members in order to replace the loss in old ones. Consequently, we will have to continue to work hard for a long time to come. We can and will solve this problem, eventually.

B. Nominations and Elections

The nominating committee was composed of L. H. Snyder, C. Nash Herndon, and S. C. Reed. The candidates were well liked and the voting close. The following were elected:

President—C. P. Oliver
Vice President—James V. Neel
For two year terms
Directors at large—Madge T. Macklin
Eldon J. Gardner
Clarke Fraser

C. Proposed Amendments to the Constitution

1. To amend Article V, Sec. 6 which reads "A majority of the Board of Directors shall constitute a quorum for transacting business." As amended, this would read, "A quorum for transacting business shall consist of those members of the Board present at the official meeting."

The reason the Board of Directors suggests this change is that, under the present article, a quorum consists of seven out of the thirteen directors. The risk that this number may fail to appear is sufficiently great to warrant this change to a more elastic system.

2. To amend Articles IV and VI to provide for the inclusion of a President-elect among the officers and as a member of the Board of Directors. Changes are additions, and are underlined.

Article IV, Sec. 1 to be amended to read, "The officers of the Society shall consist of a President, *a President-elect*, a Vice-president, a Secretary, a Treasurer, and an Editor."

Article IV, Sec. 2 to be amended to read, "*The President-elect* and the Vice-president shall be elected for a term of one year and may not be re-elected to the same office. *The President-elect becomes the President automatically following the expiration of the President's term of one year. The Vice-*

president assumes the office of President whenever it is necessary to fill the unexpired portion of the President's term of one year."

Article VI, Sec. 1 to be amended to read, "Two candidates for each office, *except that of the President,* and two candidates for each of the directorships to be elected shall be nominated by the nominating committee, with due consideration being given to representation of the several fields of interest of the Society.

The amendments are submitted for discussion and will be voted upon by the membership at the next annual meeting.

Respectfully submitted,

SHELDON C. REED
Secretary

THE AMERICAN SOCIETY OF HUMAN GENETICS

PUBLISHERS OF THE AMERICAN JOURNAL OF HUMAN GENETICS

MEMBERSHIP LIST—SEPTEMBER 1, 1952

The secretary welcomes corrections of spellings and addresses. Positions, titles and degrees, except for that of M.D. or D.D.S. are omitted to save printing expenses. Inclusion of the M.D. degree permits an estimate of the proportion of the members of the Society who are physicians.

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